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Title of Dissertation: "*Helicobacter Pylori* Transmission and Risk Factors for Infection in Rural China"

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8 December 1999

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Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE <b>1999</b>		2. REPORT TYPE		3. DATES COVERED <b>00-00-1999 to 00-00-1999</b>	
4. TITLE AND SUBTITLE <b>Helicobacter Pylori Transmission and Risk Factors for Infection in Rural China</b>				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) <b>Uniformed Services University of the Health Sciences,F. Edward Hebert School of Medicine,4301 Jones Bridge Road,Bethesda,MD,20814-4799</b>				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT <b>Approved for public release; distribution unlimited</b>					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT <b>see report</b>					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES <b>223</b>	19a. NAME OF RESPONSIBLE PERSON
a. REPORT <b>unclassified</b>	b. ABSTRACT <b>unclassified</b>	c. THIS PAGE <b>unclassified</b>			

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## ABSTRACT

Title of Dissertation: *Helicobacter pylori* Transmission and Risk Factors for Infection in Rural China

Name, degree, year: Linda Morris Brown, Dr.P.H., 1999

Thesis directed by: Terry L. Thomas, Ph.D., Associate Professor, Department of Preventive Medicine & Biometrics

*Helicobacter pylori* (*H. pylori*) is one of the most common bacterial infections among humans, but little is known about its mode of transmission. A cross-sectional study of 3288 adults aged 35-69 from Shandong Province, China was conducted to assess some possible risk factors that may be associated with *H. pylori* infection in this high prevalence area of China. In-person home interviews (lasting approximately 15 minutes) were conducted in Chinese from October 1997-May 1998. The response rate was 96.4%. Maximum likelihood estimates and bootstrap confidence intervals (CI) of the association between the prevalence of *H. pylori* infection and demographic, lifestyle and some common environmental exposures were computed using polychotomous logistic regression.

The *H. pylori* serostatus of the study participants was positive 60.6%, negative 31.0%, and indeterminate 8.4%. Source of drinking water, especially water from a shallow village well (OR=1.8, 95%CI=1.4-2.3), was associated with increased prevalence of *H. pylori* infection. ORs were also elevated for infrequent hand washing before meals (OR=1.6, 95%CI=1.0-2.5 ) and bathing in a pond or ditch (OR=1.6, 95%CI=1.0-2.4). ORs were also associated with median village education level, ranging from 1.0 for villages classified as high, to

1.7 (95%CI=1.4-2.1) for villages classified as medium, to 2.4 (95%CI=2.0-3.0) for villages classified as low. ORs decreased slightly with increased consumption of all allium vegetables combined. The ORs were reduced for having a cat as a pet during childhood (OR=0.7, 95%CI=0.5-1.0) and/or adulthood (OR=0.6, 95%CI). No significant associations were seen with any measure of cigarette smoking or alcoholic beverage consumption. Additionally, crowding or density factors as a child were not related to a higher prevalence of *H. pylori* infection as an adult.

The results of the multi-variate modeling revealed prevalence rates that ranged from 75% to 46%, prevalence rate ratios that ranged from 1.0-1.5, and relative odds ratios that ranged from 1.0-8.6. Although a lack of heterogeneity in the population may have hampered the ability to detect actual associations, the finding that water may contribute to *H. pylori* infection deserves further evaluation. It is also noteworthy that cat ownership was not associated with an increased prevalence of *H. pylori*. The results of this study suggest that person-to-person and waterborne transmission, but not zoonotic transmission, are likely routes of *H. pylori* infection in this rural Chinese population.

***HELICOBACTER PYLORI* TRANSMISSION  
AND RISK FACTORS FOR INFECTION  
IN RURAL CHINA**

by

**Linda Morris Brown**

**Dissertation submitted to the Faculty of the  
Department of Preventive Medicine and Biometrics of the  
Uniformed Services University of the Health Sciences  
in partial fulfillment of the requirements for the degree  
of Doctor of Public Health 1999**

## ACKNOWLEDGMENTS

I thank my advisor Dr. Terry Thomas and the other members of my dissertation committee - Drs. David Cruess, Andre Dubois, Gary Gackstetter, and Mitchell Gail for their advice and helpful comments; my colleagues at the National Cancer Institute - Drs. Joseph F. Fraumeni, Jr., Mitchell Gail, Frank Groves, and Wei-cheng You for their technical and administrative support; my colleagues at the Beijing Institute for Cancer Research - Drs. Yunsheng Chang, Wei-dong Liu, Jun-Ling Ma, Kai-feng Pan, and Lian Zhang for their technical assistance and management of field activities; John Heinrich (Westat, Inc.) for his assistance in data file management; Stella Semiti and Jerome Mabi (Information Management Systems) for computer support; and the residents of the 13 Linqu villages who participated in this study.

## DEDICATION

To Richard, Leslie, Jeffrey, and Rocky for their support and understanding.



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## **CHAPTER I. BACKGROUND AND RATIONALE**

### **BACKGROUND**

*Helicobacter pylori* (*H. pylori*) is one of the most common bacterial infections in humans worldwide,<sup>1</sup> and remains a public health problem in both developed and developing countries.<sup>2</sup> This spiral-shaped bacterium present on human gastric mucosa was first isolated in 1982 by Warren and Marshall.<sup>3</sup> Initially it was classified as *Campylobacter pylori*, but in 1989 was included in a new genus, *Helicobacter* and renamed *Helicobacter pylori*.<sup>4</sup> Since its discovery, *H. pylori* has been recognized as a major cause of gastritis, and a risk factor for duodenal ulcer disease, gastric ulcer disease, and gastric lymphoma in humans.<sup>5,6</sup> Additionally, the International Agency for Research on Cancer (IARC) Working Group concluded in June 1994 that there was sufficient evidence to consider *H. pylori* a human carcinogen for gastric cancer.<sup>7</sup> However, some researchers now believe that the epidemiologic evidence is contradictory and that IARC was premature in its Group 1 designation because *H. pylori* appears to play a role only in the initial steps that result in chronic inflammation (a common occurrence in much of the world), but not in the later steps that lead to carcinogenesis.<sup>8,9</sup>

### **Modes of transmission**

Despite the worldwide interest in *H. pylori* infection and its sequelae, little is known about its mode of transmission. Most epidemiologic data support a

person-to-person mode of transmission (oral-oral, fecal-oral, or gastro-oral). This mode of transmission is further supported by the discovery of *H. pylori* in saliva, dental plaque, feces, and vomitus, but the details of transmissibility of *H. pylori* infection from these sources is not known. There has also been some support for water and sewage-born transmission. Although the principle reservoir for *H. pylori* infection appears to be the human stomach, *H. pylori* has been isolated from monkeys, baboons, and domestic cats. Knowledge of the manner of *H. pylori* transmission is fundamental to the development of strategies for controlling and eventual eradication of this infectious disease.

## **Epidemiology**

Because acute infection with *H. pylori* is generally asymptomatic, it is not possible to ascertain when infection occurs using clinical criteria.<sup>10</sup>

Epidemiologic studies of the prevalence of *H. pylori* are usually conducted by using serologic tests that detect IgG or IgA antibodies to *H. pylori* infection or by <sup>13</sup>C urea breath tests (UBT) that detect urease activity produced by the bacteria.<sup>11</sup>

Although a few studies have attempted to estimate incidence rates and seroconversion rates by looking at serial serologic surveys within a population, most of the information on the epidemiology and rates of *H. pylori* infection in geographically and demographically diverse populations comes from sero-prevalence studies. Studies of *H. pylori* prevalence have generally been cross-sectional in design and have included random surveys of the general population,

groups of healthy volunteers, military recruits, groups of hospitalized or institutionalized children and adults, or adults attending outpatient clinics. In addition, a number of studies have investigated intra-familial clustering of *H. pylori* infection and infection patterns in infants.

The prevalence of *H. pylori* in developing countries may reach more than 70% compared with less than 40% in developed countries. *H. pylori* infection varies widely by geographic area, age, race, and socioeconomic status (SES). Residence in a developing country, increasing age, black or Hispanic ethnicity, and lower education and income have been associated with higher *H. pylori* prevalence. Low SES during childhood, child feeding practices such as premastication of food by the mother, and poor sanitation/hygiene have been implicated.

## **RATIONALE**

Since 1983 the National Cancer Institute (NCI) has been collaborating with the Beijing Institute for Cancer Research (BICR) and School of Oncology, Beijing Medical University to assess reasons for the exceptionally high rates of stomach cancer in Linqu, a rural county in Shandong Province in northeast China with high prevalences of precancerous gastric lesions.<sup>12</sup> Because Linqu county also has high rates of *H. pylori* infection,<sup>13</sup> it was an ideal area to conduct research into the etiology of *H. pylori* infection and its possible mode(s) of transmission.

A population-based sample with known *H. pylori* status was assembled from 13 randomly selected Linqu villages enrolled in a randomized intervention trial to inhibit progression of precancerous gastric lesions. This stable population was used to evaluate etiologic factors that influence the prevalence of *H. pylori* infection in Shandong Province, China. The study was established to measure factors characteristics of both the environment and the host. Factors of particular interest include measures of adult and childhood socioeconomic status, source of water, personal hygiene, sharing of utensils, potential food contamination, and exposure to animals.

### **Research questions**

The specific aims of the study were to determine whether there is an association between *H. pylori* sero-positivity and

- (1) drinking water source (i.e., shallow well, deep well, pond, river, ditch, or running water), storage, or treatment;
- (2) adult sanitation and hygiene (e.g., hand washing, use of soap, bathing, teeth brushing, and sharing of cups);
- (3) social class factors;
- (4) use of tobacco or alcohol products;
- (5) presence of gastro-esophageal reflux;
- (6) raw fruit and vegetable consumption or preparation (i.e. washing or peeling);
- (7) adult exposure to pets and other domestic animals;
- (8) childhood exposures (e.g. domestic animals, crowding, and eating premasticated food).

## CHAPTER II. LITERATURE REVIEW

### INTRODUCTION

*Helicobacter pylori* (*H. pylori*), a spiral-shaped pathogenic bacterium found on the human gastric mucosa, was first isolated by Warren and Marshall in 1982<sup>3</sup> and soon after linked with chronic antral gastritis and peptic ulceration.<sup>14</sup> Initially it was classified as *Campylobacter pylori*, but in 1989 was included in a new genus, *Helicobacter* and renamed *Helicobacter pylori*.<sup>4</sup> Although it has been less than twenty years since its “discovery”, thousands of articles have been written about *H. pylori*, one of the most common human bacterial infections in the world.<sup>1</sup> Since a complete review of all the *H. pylori* literature is beyond the scope of this dissertation, this paper will include brief reviews of the microbiologic characteristics of *H. pylori*, the diagnostic tests utilized in epidemiologic studies, and the association of *H. pylori* with gastric cancer and other diseases. The primary focus will be on the epidemiology and transmission of *H. pylori* infection in adults including reviews of *H. pylori* prevalence in various countries, risk factors for *H. pylori* infection, and hypothesized modes of transmission. Studies of children will be added where appropriate to supplement the adult literature. The major emphasis will be on scientific articles from the recent literature from 1995 through mid 1999, but selected scientific papers published in peer-reviewed journals prior to 1995 will also be included.

## MICROBIOLOGIC CHARACTERISTICS

*H. pylori* is an S-shaped or curved gram-negative rod. It has from two to six flagella that give it the mobility to withstand rhythmic gastric contractions and penetrate the gastric mucosa. It measures 2.4-4.0  $\mu\text{m}$  in length and 0.5-1.0  $\mu\text{m}$  in width. The principle reservoir for *H. pylori* infection appears to be the human stomach, especially the antrum. However, it does not colonize areas of the stomach where intestinal metaplasia or dysplasia are present.<sup>15</sup> *H. pylori* contains a large urease enzyme protein that produces urease which allows the organism to survive in the acidic stomach by creating an alkaline environment. *H. pylori* produces a number of virulence factors including cytotoxin associate gene A (*cagA*) and vacuolating cytotoxin (*vacA*) that may be associated with pathologic mechanisms.<sup>16,17</sup> Approximately 10-20% of the population appear resistant to chronic infection with *H. pylori*.<sup>18</sup> Chronic infection appears to be influenced by host genetic factors or markers such as ABO blood group and Lewis blood-group antigen,<sup>19</sup> and to differences in susceptibility to particular strains of *H. pylori*.<sup>20</sup> *H. pylori* also has a dormant coccoid form that it reverts to when faced with unfavorable environmental conditions.<sup>15</sup>

## DIAGNOSTIC TESTS USED IN EPIDEMIOLOGIC STUDIES

Because acute infection with *H. pylori* is generally asymptomatic, it is not possible to ascertain when infection occurs on symptomatic or clinical grounds.<sup>10</sup> Most epidemiologic studies of the prevalence of *H. pylori* infection usually

employ serologic tests or  $^{13}\text{C}$  urea breath tests (UBT). Biopsy-based methods are often utilized in hospital or clinical settings.

### **Biopsy-based diagnostic tests**

In the early 1990's, the diagnosis of *H. pylori* infection was based on either the isolation of bacteria from gastric biopsy specimens obtained from endoscopy or by identification of the bacteria on stained biopsy sections.<sup>14,21</sup> Today, a positive culture obtained from endoscopy is usually augmented with a biopsy urease test (CLO test) and/or histology is often used as a “gold standard” to diagnose patients with active *H. pylori* infection.<sup>22,23</sup> While biopsy/culture is 100% specific, it is not 100% sensitive; this method can evaluate only a relatively small portion of the stomach; it is not able to differentiate among the various strains of *H. pylori*; and it is highly invasive and expensive.

### **Serologic tests**

In 1988 Perez-Perez et al, developed a non-quantitative, enzyme-linked immunosorbent assay (ELISA) to detect *H. pylori* antibodies in serum.<sup>21</sup> A major advantage of this serologic test is that it allows large numbers of subjects to be screened quickly and relatively inexpensively, thus it is a good test to use in epidemiologic studies.<sup>24</sup> The prevalence of *H. pylori* (in either fresh or stored serum) is usually found by using serologic tests that detect IgG antibodies to *H. pylori* infection, although IgA and IgM antibodies have also been utilized.<sup>25</sup>

There are, however, several limitations to the use of serologic tests. 1) Since no single antigen is recognized by sera from all subjects, antigen reagent preparations should contain multiple strains of *H. pylori*.<sup>26,27</sup> It has also been suggested that assays based on indigenous strains may perform better.<sup>28</sup> In fact, a study in Henan Province, China found a much higher prevalence of *H. pylori* using a biopsy-based technique (85.6%) than using serology (56.2%).<sup>29</sup> The authors noted that one explanation for the large discrepancy may be that the antigen used for serology was derived from a single *H. pylori* strain isolated in Germany. However, other studies have found little difference in outcome between local and referent strains.<sup>30,31</sup> 2) It is difficult to define the cut-off value that divides positive from negative subjects. One approach to improve both sensitivity and specificity, although this biases both values upward, is to include a gray or indeterminate zone for subjects whose values can not be considered truly positive or truly negative. In an epidemiologic study comparing the characteristics of positive and negative subjects, such an approach would help to minimize misclassification by not including those with equivocal results. An ROC (receiver operating characteristic) is often used to determine the effect on the test of varying the cut-off value or to compare the performance among different tests.<sup>23</sup> 3) The test is sensitive to changes in reagents and laboratory conditions; thus sera collected at different points in time (e.g., before and after treatment or longitudinally at yearly intervals) should be run together in the same ELISA plate. 4) Serology is not an appropriate test to use immediately following treatment for *H. pylori*. It takes a variable amount of time (anywhere from 6 months to two



years or in some cases never) for an elevated serum IgG value to return to baseline values. Some researchers suggest considering IgG values that have fallen by 50% or more six months after treatment as an indication of successful *H. pylori* eradication.<sup>26,32</sup>

### **Breath Test**

The UBT using either  $^{13}\text{C}$  or  $^{14}\text{C}$  is a noninvasive, non-quantitative test that determines current *H. pylori* status by detecting urease activity produced by the bacteria. This test has recently been approved by the FDA for routine use. Although not universal, several researchers now consider the breath test a non-invasive “gold standard”.<sup>23,26</sup> Generally, this is a useful test to use following antibiotic treatment since gastric urease is only present in the stomach when the bacteria that make the urease are present. However, false negatives can result in treated subjects if bacteria are present in too small a number to produce detectable urease. For the small percentage of people infected by other bacteria that also produce urease (generally less than 5% in most populations), false positives can result. UBT is generally more expensive than serology, but its use in epidemiologic studies, especially studies utilizing children as study subjects, is increasing.

### **DISEASE ASSOCIATIONS**

*H. pylori* is thought to be indigenous to the human population and is well-adapted to exist in the human stomach for the lifetime of its host.<sup>16</sup> Spontaneous

eradication of *H. pylori* from the gastric mucosa, as measured by sero-reversion, is a relatively rare event; 0.1-1.1% annually.<sup>33</sup> Infection with *H. pylori* can result in chronic gastritis, a cellular infiltrate of immunocompetent lymphocytes, and IgA, IgG, and IgM-secreting plasma cells in the gastric mucosa.<sup>34</sup> Infection is generally asymptomatic with only a small percentage of those infected developing clinical disease.<sup>35</sup> *H. pylori* has been recognized as a major cause of gastritis and is associated with duodenal ulcer disease, gastric ulcer disease, and gastric lymphoma in humans.<sup>5,6</sup>

Environmental and host genetic factors appear to be important in the progression of *H. pylori* initiated gastritis into more serious outcomes. Additionally, variation in age at acquisition of *H. pylori* has been proposed as a possible factor to explain the observation that the same organism, *H. pylori*, apparently produces different effects on the gastric mucosa that result in different clinical outcomes.<sup>6</sup> According to a hypothesis proposed by Blaser et al., early age at acquisition of *H. pylori* infection may result in more intense inflammation and the early development of atrophic gastritis and subsequent risk of gastric ulcer and/or gastric cancer.<sup>36</sup> Later acquisition of infection would induce a different series of gastric changes that would favor the development of duodenal ulcer.<sup>36</sup> High rates of gastric cancer in areas where infection is common in early childhood support this hypothesis. Other host and environmental factors such as hygiene practices and diet may also play a role in the acquisition of infection and the expression of clinical disease.<sup>18</sup>

The model of gastric cancer postulated by Correa suggests a progression from chronic gastritis to gastric atrophy, to intestinal metaplasia, to dysplasia, to cancer.<sup>37</sup> In 1991, nested case-control studies of gastric carcinoma in the United States and Britain suggested that *H. pylori* may be a cofactor in the pathogenesis of gastric cancer.<sup>38-40</sup> Recent investigators have continued to find an increased risk of non-cardia, gastric cancer in *H. pylori* positive compared with *H. pylori* negative subjects.<sup>41,42</sup> An International Agency for Research on Cancer (IARC) Working Group felt that there was sufficient evidence in 1994 to classify *H. pylori* as a human carcinogen for gastric cancer.<sup>7</sup> However, some researchers now believe that the epidemiologic evidence is contradictory and that IARC was premature in its Group 1 designation because *H. pylori* appears to play a role only in the initial steps that result in chronic inflammation (a common occurrence in much of the world), but not in the later steps that lead to carcinogenesis.<sup>8,9,43</sup> Intervention studies that include treatment for *H. pylori* for subjects at different stages in the progression toward cancer will be informative in clarifying the "*H. pylori* = gastric cancer" controversy.

On the other hand, some *H. pylori* strains, particularly *cag+*, appear to be protective against adenocarcinomas of the esophagus and gastric cardia.<sup>41,44,45</sup> Also, the prevalence of *H. pylori* infection appears to be lower in persons with gastroesophageal reflux disease (the major risk factor for Barrett's esophagus which is strongly associated with adenocarcinoma of the esophagus) than in controls.<sup>46,47</sup>

Recently, there has been some concern that *H. pylori* infection may be associated with increased risk of coronary heart disease possibly due to a low-grade systemic inflammatory response or an increase in concentrations of circulating coagulation factors.<sup>48-50</sup> However, the results from several prospective studies,<sup>48,51,52</sup> and a meta analysis of more than 20 epidemiological studies<sup>53</sup> suggest that *H. pylori* is probably not an important contributor to coronary heart disease.

## **EPIDEMIOLOGY**

### **Descriptive studies/Prevalence**

*H. pylori* infection is ubiquitous and a public health problem in both developed and developing countries. The prevalence of *H. pylori* infection varies widely by geographic area, age, race, and socioeconomic status (SES). Because it is not possible to ascertain when infection occurs on clinical grounds, most of the information on the rates of *H. pylori* in geographically and demographically diverse populations comes from sero-prevalence studies. This has major disadvantages for epidemiologists since it is generally not possible to distinguish between factors associated with acquiring versus maintaining *H. pylori* infection.<sup>54</sup> Studies of *H. pylori* prevalence among adults have generally been cross-sectional in design and have included random surveys of the general population,<sup>13,25,48,55-70</sup> groups of healthy volunteers,<sup>71-81</sup> military personnel,<sup>82-84</sup> students,<sup>85,86</sup> employed workers,<sup>54,87,88</sup> groups of institutionalized patients,<sup>89-92</sup> or patients attending hospitals or out-patient clinics.<sup>29,49,93-101</sup> Included in Table II-1

is the prevalence of *H. pylori* in adult populations from various geographic areas of the world.

*H. pylori* prevalence in developing countries may reach 70% or more compared with 40% or less in developed countries. The acquisition rate of *H. pylori* appears to be more rapid in developing than developed countries.<sup>69,102</sup> In a rural village of Linqu County, Shandong Province, China, a study of 98 children noted that nearly 70% of children aged 5-6 years were infected with *H. pylori*,<sup>103</sup> a rate similar to that reported for adults in that area,<sup>13</sup> suggesting that most infection takes place early in childhood. Since the annual rate of seroconversion in adult populations in developed countries appears to be small (on the order of 0.2-1.0%<sup>33</sup>) the increasing prevalence by age, seen in most developed countries, is most likely due to a birth cohort effect where older populations had higher rates of infection in the past probably due to poorer sanitation.<sup>69,104-107</sup> Two recent studies of young adults, one of Israeli backpackers to Southeast Asia, South America, and Africa<sup>108</sup> and the other of military personnel deployed to the Persian Gulf for Desert Storm<sup>82</sup> found much higher annual rates of seroconversion, 6.4% and 7.3%, respectively, suggesting that adults can seroconvert at higher rates than expected under unusual circumstances.

In the United States, differences by race are evident, with whites having a substantially lower seroprevalence of *H. pylori* than either blacks or Hispanics.<sup>49,77,79,80,83,84,109</sup> In a study by Replogle et al in California,<sup>49</sup> the ORs for being *H. pylori* seropositive, given African-American and Hispanic ethnicity, were 4.1 (2.2-7.4) and 3.1 (1.6-6.2), respectively. Similar risk estimates for blacks

(OR=4.4, CI=3.0-6.3) and Hispanics (OR= 4.2, CI=2.1-8.6) were seen in a study of US Army recruits<sup>84</sup> and a study of US Navy and Marine Corps personnel<sup>83</sup> (OR=4.2, CI=2.9-6.0 for blacks; OR=3.9, CI=2.4-6.3, for Hispanics) Ethnic differences were also evident in New Zealand, where *H. pylori* was most prevalent in Pacific Islanders, intermediate in Maori, and least prevalent in Europeans<sup>88</sup> and in Belgium where Caucasians of Belgian decent (22.6%) had much lower rates than subjects who originated from the Mediterranean countries of Tunisia and Morocco ( 62.5%).<sup>99</sup> After adjusting for age and SES, the RR for Maori and Pacific Island subjects compared to Europeans were 1.4 (1.1-1.8) and 1.8 (1.4-2.2), respectively.<sup>88</sup> These differences in *H. pylori* prevalence by race/ethnicity may reflect differences in social and/or hygiene factors, or the wide-spread use of anti-microbials for treatment of other common infections, especially during childhood.<sup>110</sup> This variability may also be explained by differences in ethnic or genetic predisposition to infections.<sup>18</sup>

Although some studies reported an excess for *H. pylori* of one gender over the other,<sup>49,84</sup> overall, there are no striking gender differences in *H. pylori* prevalence. Differences in *H. pylori* prevalence by SES factors can be striking and will be presented in detail under the risk factor section. The high rates evident in institutionalized populations<sup>90-92</sup> will be discussed in relation to *H. pylori* transmission. Several factors require consideration when comparing rates of *H. pylori* positivity among studies. Antigenic responses to *H. pylori* may vary. If the antigens used in a serologic test were not specific to the population tested, then seroprevalence could be greatly underestimated.<sup>26-28</sup> In addition, differences in

seroprevalence could be due to differing test characteristics (i.e., specificity), or laboratory conditions.<sup>111</sup>

## **Risk Factors**

In addition to determining the prevalence of *H. pylori* in various geographic areas, a number of studies included a questionnaire component designed to investigate risk factors for *H. pylori* positivity. The quality of these studies was variable and in many cases the statistical procedures utilized were not well described. Also, it was not always clear whether prevalence rates for the various groups compared were standardized either directly or indirectly to adjust for differences in age structures. The most common tests used to determine statistical significance were the chi-square test (for independence and homogeneity), Fisher's exact test, and the Student's t test. Crude and adjusted relative risks (RRs) and odds ratios (ORs) were calculated using the Mantel-Haenszel procedure and unconditional logistic regression, respectively. ORs were the most common measure of association presented.

While the OR is a legitimate measure of association in its own right, it can be used as an estimate of the RR only when the incidence of disease in the population studied is rare. In addition, the cases and noncases included in the study should be representative of all cases and noncases in the population from which the study subjects came. Because this "rare disease assumption" does not hold for *H. pylori* infection in any of the populations studied, the OR should not be considered an approximation of the RR for studies of *H. pylori*. In

addition, since these are cross-sectional studies, the outcome measure is prevalence of *H. pylori* infection at the time blood was drawn for serology, biopsy and culture were performed, or the breath test samples obtained. Thus, the measure of association in a logistic regression model is the prevalence odds ratio which compares the odds of being infected with *H. pylori* in the exposed to the odds of being infected with *H. pylori* in the unexposed/referent group.

Described in subsequent tables and text are the major factors investigated for their possible association with *H. pylori* positivity. The following topics are included: smoking, alcohol use, diet, occupational exposures, waterborne exposures, exposure to pets and other animals, hygiene practices, density/crowding, social factors, and family history of gastric disease/ulcer.

### **Smoking**

Table II-2 presents a summary of results from several recent studies that evaluated the possible association between *H. pylori* infection and smoking. Whereas studies by Lin et al,<sup>57</sup> Zober et al,<sup>112</sup> Hamajima et al,<sup>113</sup> Murray et al,<sup>61</sup> Fontham et al,<sup>109</sup> and Bateson<sup>114</sup> found *H. pylori* sero-positive subjects overall more likely to be current smokers than sero-negative subjects, their results were often not consistent by race or gender. For example, the study by Hamajima et al found an OR of 7.8 for *H. pylori* infection among current male smokers, but only an OR of 1.2 among female current smokers.<sup>113</sup> Conversely, the study by Lin et al, found a significant association with current smoking among females (OR=2.8), but not among males.<sup>57</sup> The positive finding (OR=1.7) reported by



Fontham et al held for blacks (OR=3.1), but not whites (OR=0.6)<sup>109</sup> and the study by Lin et al found no association with intensity or age started smoking.<sup>57</sup> At least 12 recent studies found no significant association with current smoking or any other measure of tobacco use.<sup>13,54,63-65,68,75,88,92,115,116</sup> and one recent study from Japan found a significant negative association with current smoking.<sup>87</sup> Some authors have suggested that these contradictory results may be due to uncontrolled confounding by social class<sup>61,87</sup> or to differential antibiotic use since smoking appears to effect treatment success.<sup>113</sup> While one can not rule out that an association between smoking and *H. pylori* infection may exist, such a hypothesis is not strongly supported by the current literature.

### **Alcohol use**

The results from recent epidemiologic studies looking at the relationship between alcohol consumption and *H. pylori* infection are presented in Table II-3. None of the studies found a positive association between alcohol consumption and *H. pylori* infection, but many noted a non-statistically significant reduction in risk. The studies by Brenner et al, that incorporated a quantitative measure of alcohol consumption, while controlling for potential confounding factors, found a significant negative association with alcohol consumption, especially at moderate to high levels.<sup>115,117,118</sup> In two of these studies, the association was stronger for wine than beer.<sup>117,118</sup> Several studies did not adequately control for potential confounding variables or did not present the actual risk estimates or prevalences in their papers, thus it is difficult to evaluate whether alcohol consumption has a

“protective” effect on the prevalence of *H. pylori*. *H. pylori* is better able to survive in the acid environment of the stomach than other bacteria due to its production of urease. Therefore, it is not surprising that the reduction in gastric pH which may accompany alcohol intake, would have little effect on the prevalence of *H. pylori*.<sup>119</sup> However, alcohol is known to possess direct antimicrobial properties that appear to be greater for wine than for other types of alcoholic beverages.<sup>120</sup> The differing results may be due to the different methodologies employed or to real differences in either the type/amount of alcohol consumed and its effect on *H. pylori* in different populations.

### **Diet**

Dietary associations with *H. pylori* are presented in Table II-4. Although the studies cover many different types of populations and include studies of both adults and children, there are some consistent associations that suggest that nutritional status may be related to *H. pylori* infection. Goodman et al<sup>121,122</sup> and Fontham et al<sup>109</sup> found significantly reduced ORs and negative gradients in risk of *H. pylori* infection with increased consumption of fruits and/or vegetables. An intervention study by Jarosz et al found that 30% of *H. pylori* infected patients with chronic gastritis treated with vitamin C for four weeks had apparent *H. pylori* eradication compared with 0% in the control group.<sup>123</sup> Trends of decreasing risk with increasing consumption of vitamin C was observed in studies by Goodman et al<sup>121</sup> and Fontham et al;<sup>109</sup> however, Malaty et al found high levels of vitamin C to be associated with *H. pylori* infection in twins reared apart.<sup>124</sup> Goodman et al

also found high levels of beta-carotene to be protective.<sup>121</sup> In contrast, consumption of raw/uncooked vegetables was related to risk of having *H. pylori* infection in studies by Goodman et al (OR=2.0 for 3 or more servings per day)<sup>122</sup> and Hopkins et al (OR=3.2).<sup>125</sup> The cause of this increased risk has not been determined, but may have been due to contaminated water or soil,<sup>125</sup> or contamination by a vector such as the housefly.<sup>126</sup> The role of food prepared under less than ideal sanitary conditions as a possible mechanism of *H. pylori* transmission, was suggested by Begue et al who found elevated risks for consumption of food obtained from street vendors in Peru.<sup>127</sup>

### **Occupational exposures**

Occupational exposures were considered by several researchers (Table II-5) investigating whether people working in certain occupations with potentially greater exposure to *H. pylori* had increased prevalence of infection. Bohmer et al in a study of inhabitants of institutions for the intellectually disabled found that most of the patients were seropositive (82.8%).<sup>90</sup> He also reported a higher rate of seropositivity (31.6%) among employees such as the nursing staff with intensive contact with institutionalized inhabitants than among employees such as medical staff, speech-trainers, secretarial staff, and drivers with little or no direct contact (14.1%).<sup>90</sup> Risk of infection from potential exposure to these bacteria in waste water was investigated by Friis et al in a study of Swedish sewage workers.<sup>128</sup> They found that seroprevalence did not differ between sewage workers and other age-SES-location-matched municipal workers.<sup>128</sup>

Shelly and Haddadin reported that *H. pylori* infection did not appear to be an occupational hazard for anesthesiologists in the U.S. even though they are potentially exposed to secretions from the stomachs of their patients while performing endotracheal intubations.<sup>129</sup>

Since *H. pylori* has been cultured from both saliva and dental plaque, studies were conducted by Lin et al,<sup>130</sup> Banatvala et al,<sup>131</sup> and Malaty et al<sup>132</sup> to determine whether dentists, dental nurses, and dental workers were at increased risk for *H. pylori* infection. Dentists and dental workers were not found to have higher rates of seropositivity than controls in any of these studies. When Lin et al compared the prevalence of *H. pylori* in dentists and dental nurses to that in endoscopists and endoscopy nurses they found endoscopists (80%) to have significantly higher rates than dentists (21%), but the rates in the two types of nurses were not significantly different.<sup>130</sup>

There has been conflicting data regarding the prevalence of *H. pylori* in endoscopy staff. In a group of eleven studies that focused on this occupation, four found that medical staff who performed endoscopies had a higher prevalence of *H. pylori* than medical staff who did not<sup>133-136</sup> and three reported the prevalence of *H. pylori* to be significantly higher in endoscopists compared to population controls.<sup>137-139</sup> The results of a recent study by Mones et al in Spain that used the UBT indicated that medical professionals, more specifically gastroenterologists performing endoscopies, do not have a higher prevalence of *H. pylori* infection than do healthy controls.<sup>140</sup> Braden et al found no increased risk of *H. pylori* infection in endoscopy staff (physicians and nurses) compared to

the general medical staff (physicians and nurses), but did find a risk for all medical staff compared to controls.<sup>141</sup> On the other hand, Rudi et al found that neither exposure to patients in an acute care hospital (Group 2) nor exposure to endoscopic procedures (Group 3) increased the rate of *H. pylori* infection.<sup>116</sup> In a study published by Nishikawa et al, *H. pylori* overall seroprevalence among endoscopists and endoscopy nurses did not differ significantly from that in healthy controls, although the prevalence among younger (<40 years old) endoscopy staff was significantly higher than among younger controls (24.4% vs 12.0%,  $p < 0.05$ ).<sup>142</sup> It is possible that differences in medical practices, including the use of gloves and other protective equipment, may be responsible for these discrepancies. To obtain a more definitive answer, a large prospective study of endoscopists would be required.<sup>143</sup> The probable risk for endoscopists, but not dentists suggests that gastric mucous may be a better medium for transmission of *H. pylori* than saliva.<sup>133</sup>

### **Waterborne Exposures**

Water has been suggested as a possible source of *H. pylori* infection. Recent studies that accessed the relationship between *H. pylori* and waterborne exposures are listed in Table II-6. Studies in Columbia, rural China, and Lima, Peru found that water source may be related to risk of *H. pylori* infection.<sup>13,122,144</sup> Three waterborne factors were linked to higher risks of *H. pylori* infection in Colombian children, drinking water from a stream, swimming in a stream, and swimming in a swimming pool.<sup>122</sup> Klein et al found that the water supply in Lima,

Peru may be vulnerable to bacterial contamination, especially if it is stored in a cistern or utilized through central community water taps.<sup>144</sup> Although not significantly different due to the small percentage of subjects reporting use of a pond or ditch as a source of drinking water, Zhang et al<sup>13</sup> found a substantially higher seroprevalence of *H. pylori* (88%) among those obtaining their water from a surface-water source compared to subjects who obtained their water from a well (73%). Other studies found no differences by water source.<sup>67,74,76,125,145</sup> These studies included work by Teh et al who found no excess risk of *H. pylori* for subjects who obtained their water from the river<sup>67</sup> and Hopkins et al who found no significant excess risk for either swimming near contaminated beaches or bathing in local rivers, irrigation ditches, or lakes.<sup>125</sup>

### **Exposure to Animals/Pets**

Table II-7 identifies studies that assessed whether exposure to pets or other domestic animals, especially cats, was related to infection with *H. pylori*. A study in Germany by Rothenbacher et al found that adults who owned a cat as a child had a significantly higher prevalence of *H. pylori*.<sup>85</sup> Most studies, however, found no association with having a pet either during childhood or as an adult.<sup>78,85,93,97,127,146</sup> and two studies in the US found pet owners to have significantly lower rates of *H. pylori* infection.<sup>80,147</sup> Although it is possible that lower rates in pet owners may be due to confounding by social class, one large population-based study in Canada that adjusted for social class found no association between pet ownership and a history of peptic ulcer disease.<sup>148</sup>

Exposure to sheep was implicated in two recent studies.<sup>122,149</sup> In a study of children from rural Columbia, Goodman et al reported that children who “played with sheep” had a higher risk of *H. pylori* infection (OR=4.5).<sup>122</sup> A study by Dore et al revealed that the prevalence of *H. pylori* was significantly higher among Sardinian shepherds occupationally exposed to sheep than among their non-exposed family members or among Sardinian blood donors.<sup>149</sup> Overall, these studies only weakly support a role for domestic pets or other animals in the transmission of *H. pylori*. In light of the interesting findings with sheep, further investigation of exposure to other domestic animals is warranted.

### **Hygiene Practices**

Presented in Table II-8 are studies that assessed the relationship between *H. pylori* infection and various hygiene practice indicators in a number of countries. Overall, poor hygiene practices, especially during childhood appear to be related to higher seroprevalence of *H. pylori*.<sup>150</sup> Some of these practices included having no WC/bathroom,<sup>73,93</sup> refrigerator,<sup>93</sup> or hot water supply<sup>73,93,100</sup> in the house when the subject was a child; sharing cups as children and having mothers who didn’t use soap when they washed their hands;<sup>122</sup> having mothers prechew the food for their young children;<sup>151</sup> use of chopsticks;<sup>63</sup> not usually washing ones hands after going to the toilet;<sup>62</sup> and living in a relatively small area with extremely limited sanitary facilities.<sup>152</sup> Other hygiene practices during adulthood such as sharing towels<sup>97</sup> and type of toilet/bathroom facilities<sup>67,73,78</sup> were not strongly related to *H. pylori* infection.

### **Density/Crowding**

A variety of density measures both during childhood and adulthood are presented in Table II-9. Some measure of overcrowding or high density during either childhood or as an adult such as living in a crowded environment,<sup>124</sup> sibship size,<sup>67,86,87,93,97</sup> number of persons or children in the home,<sup>49,55,62,73,74,122</sup> number of persons per room,<sup>60,73,78,93,100,153</sup> crowding index,<sup>77,98,147</sup> having to share a room or bed with a parent,<sup>78,85,153,154</sup> or living in a crowded space in a submarine<sup>152</sup> was consistently related to *H. pylori* positivity in all recent studies that evaluated this factor. In Japanese self-defense officials, those of lower rank stay in group barracks until they marry, thus the finding of a higher prevalence of *H. pylori* in this group may reflect crowding during young adulthood.<sup>54</sup> The positive association of *H. pylori* with high density environments, especially during childhood, suggest that crowded household quarters may facilitate the transmission of infection among siblings and other family members. This finding is consistent with the data on intrafamilial clustering of *H. pylori* presented in Table II-13.

### **Social Factors**

Studies assessing the relationship between *H. pylori* infection and social factors are presented in Table II-10. Social factors were independently associated with *H. pylori* status in a variety of studies throughout the world. The most commonly used measures were SES-based occupation (usually based on



the Registrar General's categories that separated jobs into professional occupations, managerial occupations, skilled occupations, semiskilled occupations, and unskilled occupations), education, and income. Occupation-based SES was associated with *H. pylori* seroprevalence in studies in Ireland,<sup>61,66,72,153</sup> Italy,<sup>93</sup> South Wales,<sup>48</sup> New Zealand,<sup>88</sup> and the UK, in a study by Webb et al,<sup>78</sup> but not one by Mendall et al.<sup>100</sup> Income was related to *H. pylori* infection in Australia,<sup>57</sup> Brazil,<sup>59</sup> Russia in children, but not adults,<sup>98</sup> and the US,<sup>84,147</sup> but not in Taiwan.<sup>67</sup> Low education was significantly related to higher risk of *H. pylori* in many,<sup>49,60,62,63,68,79,80,85</sup> but not all studies.<sup>65,86,88</sup> Low SES as defined differently by various investigators was also associated with a higher seroprevalence of *H. pylori* in most studies in which it was evaluated.<sup>54,74,77,124,125</sup> In Japanese self-defense workers, low rank was associated with less education and lower incomes than the middle and high ranks.<sup>54</sup>

Although social class has consistently been linked to *H. pylori* in a number of studies, it is probably not a risk factor in itself, but rather represents differences in a number of lifestyle factors that are related to risk of *H. pylori* infection. In other words, low social class whether measured by occupation, education, or income is a surrogate marker for a set of negative environmental characteristics such as poor housing, poor hygiene, unemployment, access to medical care, stressful home or work environments, poor nutrition, or exposure to other infectious agents that may increase the likelihood of an individual being exposed to *H. pylori* and may render an individual more susceptible to *H. pylori* infection if exposed. In addition, social class measures reflect differences in

economic, political, or cultural indicators that may differ between racial and ethnic groups.

### **Family History of Gastric Disease/Ulcer**

The seven studies that evaluated the relationship between *H. pylori* infection and family history of gastric disease/ulcer are presented in Table II-11. The results are generally inconclusive. Whereas the study by Brenner et al found a significantly elevated risk in children whose mothers, but not fathers had ulcer disease,<sup>155</sup> the study by Kikuchi et al found a significantly elevated risk in public service workers whose father, but not mother had a history of ulcer disease.<sup>87</sup> The study by Gasbarrini et al found significantly elevated risks of *H. pylori* infection for subjects whose siblings, but not parents had a history of ulcer disease<sup>64</sup> and the study by Martin-de-Argila et al reported a significantly greater percentage of *H. pylori* positive than *H. pylori* negative subjects with a first degree relative with peptic ulcer disease.<sup>75</sup> The other three studies listed in Table II-11 found no significant association between *H. pylori* infection and family history of ulcer.<sup>65,73,145</sup>

## **POSSIBLE ROUTES OF TRANSMISSION**

### **Person-to-Person Transmission**

#### **Institutionalized Populations**

Studies assessing the relationship between *H. pylori* infection and institutionalized populations are listed in Table II-12. The study of

institutionalized young mentally and physically handicapped adults in Austria by Lambert et al was one of the first to investigate the prevalence of *H. pylori* infection in institutionalized patients as a way to evaluate the possibility of person-to-person transmission of *H. pylori*.<sup>92</sup> He found a much higher prevalence of *H. pylori* in residents in 1989 (75%) compared to age-sex-matched controls (23%) and to stored serum taken from the same subjects in 1977 (34%). The prevalence of infection was related to length of stay in 1977, but not in 1989.<sup>92</sup> Fifty-one *H. pylori* negative subjects in 1977 were positive in 1989, for an annual seroconversion rate of 7.4%,<sup>92</sup> much higher than the rate of 0.2-1% typical of most developed countries.

Significantly higher rates of *H. pylori* infection were also seen in other institutionalized populations. In a study in England by Harris et al, *H. pylori* seroprevalence was higher in adult residents of a hospital for people with severe learning difficulties (87%) than for controls from the local community (41%).<sup>91</sup> However, there were no differences in *H. pylori* seroprevalence by age or duration of stay among the residents.<sup>91</sup> Bohmer et al, found a strong association between *H. pylori* positivity and length of institutionalization among adult inhabitants of two large institutes for the intellectually disabled in the Netherlands.<sup>90</sup> Risks were elevated for subjects with IQs<50 and those who regurgitated their food suggesting that these factors may increase the spread of *H. pylori* due to less than adequate sanitary practices among these residents.<sup>90</sup> In a study among Japanese patients institutionalized with neurologic impairments, Kimura et al found *H. pylori* to be significantly more prevalent

among institutionalized patients (81.1%) than among patients living at home (20%) or healthy Japanese.<sup>89</sup> Percent positivity was found to increase with both age and duration of institutionalization.<sup>89</sup> In addition, 18 of 38 seronegative patients (47.4%) seroconverted after one year.<sup>89</sup> For this population of patients, possible routes of transmission include salivary secretions or fecal-oral contamination. Among institutionalized schizophrenic patients in Belgium, the risk of *H. pylori* infection was elevated (OR=3.0, CI=1.4-7.3) compared with volunteer blood donor controls.<sup>156</sup> Again, the prevalence in patients increased with length of stay in the institution.<sup>156</sup>

Institutionalized children in Hong Kong with profound neurodevelopmental disabilities were found by Lewindon et al to have significantly higher rates of *H. pylori* infection (55.4%) than age-matched controls (8%).<sup>157</sup> In a group of normal children in Russia, Malaty et al found the prevalence of *H. pylori* infection to be greater in children from orphanages and communal apartments (64%) than in children with families (40%).<sup>98</sup> Although a common source of exposure can't be ruled out in several of these studies, they do lend support to the hypothesis that most *H. pylori* infection is transmitted person-to-person.

### **Familial Exposures**

A number of studies listed in Table II-13 looked at the relationship between *H. pylori* infection and intrafamilial clustering of *H. pylori*. Studies in Italy,<sup>158</sup> Belgium,<sup>159</sup> Austria,<sup>160</sup> and Canada<sup>161</sup> noted an increased prevalence of *H. pylori* infection in family members of *H. pylori* positive children compared to

family members of *H. pylori* negative children and/or age-matched control groups. Excess risks were found in both parents and siblings of infected children with no consistent differences apparent by gender of parent. Similarly, a higher prevalence of *H. pylori* infection in children who lived in households with *H. pylori* positive relatives was reported in studies conducted in Germany,<sup>155</sup> China,<sup>162,163</sup> Poland,<sup>150</sup> and Russia.<sup>98</sup>

Several studies evaluated intraspousal transmission of *H. pylori* infection. Singh et al in India<sup>164</sup> and Brenner et al in Germany<sup>165</sup> found a strong relationship between partner's infection status in studies conducted among couples from the general population and among employees of a health insurance company and their partners, respectively. In the Indian study, 60% of *H. pylori* positive spouses had seroconverted at the one-year follow-up.<sup>164</sup> The German study reported an increase in risk with the time lived with an infected partner.<sup>165</sup> Georgopoulous et al in Greece<sup>166</sup> and Parente et al in Italy<sup>167</sup> found higher rates among spouses in *H. pylori* positive than *H. pylori* negative patients and/or matched controls. However, in the Italian study, rates of positivity differed substantially (73% and 33%, respectively) for spouses and controls aged 20-34, but were the same (75% and 74%, respectively) for spouses and controls older than 50.<sup>167</sup> This is similar to a study by Ma et al conducted in an area of China where the overall prevalence rate of *H. pylori* in adults was high (68%) and differed little by age.<sup>103</sup> Ma et al reported no significant difference in the seroprevalence of *H. pylori* in spouses of *H. pylori* positive and *H. pylori* negative subjects.<sup>103</sup> Several studies performed DNA fingerprinting to determine the

specific strains of *H. pylori* harbored by family members.<sup>166,168-170,247</sup> They found the same strain of *H. pylori* to be present in spouses, siblings, and parents.<sup>166,168-170,247</sup>

These studies taken as a whole strongly support the concept of intrafamilial clustering of *H. pylori* infection. They suggest that either person-to-person transmission occurred in these families possibly due to close interpersonal contact, or that family members shared a genetic predisposition to *H. pylori* infection, or that family members were exposed to a common source of infection.

### **Oral-oral Route**

Many scientists have hypothesized that the oral-oral route is the most likely method of *H. pylori* transmission, especially in developed countries. Elevated prevalence of *H. pylori* within families and institutionalized populations provide support for this route of transmission. However, it is not clear whether *H. pylori* is a constant or intermittent inhabitant of the oral cavity.<sup>171,172</sup> Because there are numerous bacteria in the oral cavity that show urease activity, the specificity of urease-based tests may be too low to be useful in detecting oral *H. pylori* infection.<sup>173,174</sup> Polymerase chain reaction (PCR) is a very sensitive assay technique, but positive results can not confirm the viability of the bacteria and whether it is able to transmit disease.<sup>174</sup> Microbiological culture of *H. pylori* is still the recognized “gold standard” for the diagnosis of infection.<sup>175</sup> The most likely

routes of oral infection include saliva, dental plaque, and refluxed gastric contents or vomit.

Recent studies by Leung et al,<sup>176</sup> Li et al,<sup>177,178</sup> Namavar et al,<sup>179</sup> Shimada et al,<sup>180</sup> and Mapstone et al<sup>181</sup> have detected *H. pylori* DNA in saliva in *H. pylori* positive subjects using PCR assays. *H. pylori* has been successfully isolated from saliva by Ferguson et al<sup>182</sup> and Pytko-Polonczk et al.<sup>174</sup> However, several other researchers were not successful.<sup>179,183-185</sup> Evidence that *H. pylori* might be transmitted by saliva comes from a study by Megraud who found a higher risk of *H. pylori* associated with premastication of food by mothers in Western Africa who feed their infants (OR=2.9, CI=0.9-9.0).<sup>151</sup> In addition, Chow et al reported that Chinese immigrants in Australia who used chopsticks to eat from communal dishes had a significantly higher prevalence of *H. pylori* infection (64.8%) than those who did not (42.3%).<sup>63</sup> However, Leung et al were able to detect *H. pylori* DNA in both saliva and chopstick washings in only 1/15 subjects with *H. pylori* DNA in saliva and in only 1/45 subjects with *H. pylori* documented by UBT, suggesting that this mode of transmission is probably not common.<sup>176</sup> A study by Luzzza et al in rural Italy found no evidence to suggest that *H. pylori* and Epstein Barr Virus (the etiologic agent of infectious mononucleosis, a common infection that is transmitted by the oral-oral route) share a common mode of transmission.<sup>93</sup>

Several investigators have been successful in isolating *H. pylori* from dental plaque of infected subjects, but the percent positive has varied from 1% to 88%.<sup>173,174,185-187</sup> Other investigators have not been able to culture *H. pylori* from

dental plaque,<sup>188-190</sup> or to detect its presence using an indirect immunoperoxidase technique.<sup>191</sup> The inability of some researchers to culture *H. pylori* could be due to the presence of the viable but unculturable coccoid form of *H. pylori*, the presence of too small a number of organisms to detect, or the presence of too many other types of bacteria in the mouth that inhibit the growth of *H. pylori*.<sup>172</sup> Peach et al in a study of Australian adults selected from electoral rolls found that positive *H. pylori* status was associated with high plaque score, OR=1.7 (1.1-2.7) and visiting the dentist less than once a year, OR=4.4 (0.8-23.0).<sup>62</sup> Hardo et al in a study of dyspeptic patients in the UK found no association between *H. pylori* infection and time between visits to the dentist, number of times per week brushed teeth, oral hygiene index, and periodontal status scale.<sup>188</sup> In a study of patients with duodenal ulcer and hospital employees with and without occupational exposure to *H. pylori*, Dore-Davin et al found no correlation between *H. pylori* status as determined by PCR on saliva and dental plaque and status as determined by UBT.<sup>192</sup>

Because *H. pylori* acquisition rates are higher in children, especially in countries with less than adequate sanitation, Axon has suggested that *H. pylori* is an epidemic disease of childhood transmitted through a gastro-oral route by mucousy vomit.<sup>193</sup> Others feel that recovery of *H. pylori* in the oral cavity is most likely associated with gastroesophageal reflux or regurgitation of stomach contents.<sup>172,185,194</sup> Additional support for transmission of *H. pylori* via stomach contents comes from a case report of possible transmission of *H. pylori* infection between adults by ingestion of vomit during mouth-to-mouth resuscitation<sup>195</sup> and



from a study by Bohmer et al who found a higher prevalence of *H. pylori* among institutionalized intellectually disabled adults who regurgitated their food (OR=2.0, CI=1.1-3.6).<sup>90</sup>

### **Fecal-oral Route**

Another possible route of *H. pylori* transmission is the fecal-oral route. *H. pylori* DNA has been detected from feces of infected subjects by some researchers,<sup>179,180,196</sup> but not others.<sup>197</sup> Recently, Gramley et al found detectable *H. pylori* DNA in the feces of 73% of infected subjects.<sup>196</sup> Isolation of *H. pylori* by fecal culture, has been performed by a number of investigators from around the world.<sup>179,198,199</sup> However, isolation of *H. pylori* from feces has been problematic for some researchers, especially for those unable to obtain fresh fecal samples. Delay in processing the samples could have resulted in the small number of *H. pylori* organisms present being overgrown by other fecal bacteria or possibly the transformation of *H. pylori* into its viable but not culturable coccoid form.<sup>200</sup> Studies by Hazell et al in China<sup>201</sup> and Webb et al in the UK<sup>202</sup> noted serum antibodies to *H. pylori* and hepatitis A, a sensitive marker of fecal-oral exposure, but did not find strong evidence supporting community-wide fecal-oral spread of *H. pylori* via food or water.<sup>201,202</sup> Other studies that found elevated risks of *H. pylori* infection associated with lack of hand washing suggest that the fecal-oral route of transmission may be possible in some populations.<sup>62,122</sup>

## Waterborne Transmission

Experimental tests have shown that under physical or chemical stress *H. pylori* is able to convert into its viable, but non-culturable coccoid form.<sup>203</sup> It has also been demonstrated that *H. pylori* can live for several days in milk and tap water in its infectious bacillary form<sup>204,205</sup> and in river water for several months in its coccoid form.<sup>206</sup> Although researchers have failed to convert coccoid to bacillary form in culture,<sup>207</sup> it has not yet been determined whether *H. pylori* can revert from its coccoid to its infectious form in humans.<sup>208</sup> A study by Cellini et al found evidence of reversion in mice,<sup>209</sup> however, Eaton et al was not able to replicate this in gnotobiotic pigs.<sup>210</sup> Support for waterborne transmission comes from epidemiologic studies conducted in Columbia,<sup>122</sup> rural China,<sup>13</sup> and Lima, Peru<sup>144</sup> that found that water source may be related to risk of *H. pylori* infection. The finding of *H. pylori* positive drinking and sewage water samples by PCR assays in Peru provide additional evidence that waterborne transmission may be important in areas of the world with less than adequate water quality.<sup>204,211</sup> The possible role of waterborne transmission of *H. pylori* is further supported by a study by Baker and Hegarty in Pennsylvania.<sup>212</sup> They reported a strong association ( $p < 0.02$ ) between consumption of well water, contaminated by *H. pylori*, and *H. pylori* infection in those consuming the water.<sup>212</sup> In addition, an analysis of surface and ground water samples in Pennsylvania and Ohio found 61% of the samples to be contaminated with *H. pylori*.<sup>213</sup>

## Zoonotic/Vectorborne Transmission

Although the principle reservoir for *H. pylori* infection appears to be people, *H. pylori* has been isolated from non-human primates and domestic cats.<sup>20,214,215</sup> Human *H. pylori* has been shown to infect monkeys under controlled laboratory conditions.<sup>214</sup> However, even if *H. pylori* occurs naturally in monkeys, they are unlikely to represent a major route of transmission of *H. pylori* infection to humans since close contact between non-human primates and humans in most of the world is limited.<sup>214</sup>

Handt et al were the first to report isolation of *H. pylori* from domestic cats.<sup>215,216</sup> Their laboratory was able to experimentally infect naïve cats with *H. pylori*, to culture *H. pylori* from feline salivary and gastric sections, and to find *H. pylori* DNA in feline feces and dental plaque.<sup>217,218</sup> Although PCR cannot determine the viability of the *H. pylori* organism, these studies raised the possibility that *H. pylori* could be transmitted from cats to humans via saliva, vomit, or feces. Recently, El-Zaatari et al found no evidence of *H. pylori* infection when they examined 25 stray cats.<sup>219</sup> Instead, they reported that *H. helmanni* was the organism responsible for the chronic gastritis seen in these cats.<sup>219</sup> The epidemiologic evidence is also inconsistent. A significant association between *H. pylori* infection and cat ownership in childhood was reported in a study of adults in Germany,<sup>85</sup> but not in the U.K.<sup>220</sup> These results suggest that *H. pylori* infection is probably uncommon in cats and is probably not a major public health problem for cat owners.

Gnotobiotic pigs have been successfully infected with *H. pylori*, but there is currently no convincing evidence that swine are a reservoir for *H. pylori*, even though the monogastric pig stomach has anatomical and physiologic similarities with the human and non-human primate stomachs.<sup>214</sup> There has also been a suggestion in the epidemiologic literature that handling sheep may be a risk factor for *H. pylori* infection.<sup>122,149</sup> In addition, in Sardinia, 32 of 32 sheep were seropositive for *H. pylori*, *H. pylori* DNA was detected in the mucosal strips from the stomach of 3 of 10 sheep or lambs, and *H. pylori* DNA was present in raw sheep milk.<sup>149,221</sup>

The most recent reservoir suggested for *H. pylori* transmission is the housefly. In controlled experimental studies, Grubel et al found that houseflies infected with *H. pylori* in the laboratory could harbor viable *H. pylori* bacteria in their intestines as well as on their body hairs.<sup>222</sup> In further investigations, these researchers captured wild flies from rural, agricultural, and metropolitan areas in the U.S., Japan, Poland, and Egypt.<sup>126</sup> They found high levels of *H. pylori*-contaminated flies in Egypt (33%) and Poland (57%), areas where there is a high seroprevalence of *H. pylori* in children.<sup>126</sup> However, the investigators also uncovered high levels in California (38%), an area where the seroprevalence of *H. pylori* is not very high.<sup>126</sup> The possibility that flies could transmit *H. pylori* from contaminated feces to food or mucosal surfaces is indirectly supported by a number of epidemiologic studies in which subjects without indoor bathroom facilities, especially during childhood, had a higher seroprevalence of *H. pylori* than subjects with indoor facilities.<sup>73,78,93,122</sup> However, evidence is lacking that *H.*

*pylori* can be isolated from flies that have been in contact with *H. pylori* infected feces and that *H. pylori* can be transmitted from contaminated flies to food in a quantity sufficient to cause active infection in humans.<sup>223</sup> In a recent experimental study by Osato et al<sup>224</sup> researchers were unable to recover *H. pylori* from houseflies that were fed human feces infected with *H. pylori*. Therefore, it seems less likely that the domestic housefly serves as a major vector for *H. pylori* transmission.

### **Iatrogenic Transmission**

Endoscopy is a common medical procedure used to diagnose and manage gastrointestinal disease. Because of the complex structure of the endoscope and the difficulty in disinfecting them, the possibility of iatrogenic infection in patients following endoscopy is a potential risk factor not only for *H. pylori*, but also for other infectious diseases such as hepatitis B, hepatitis C, tuberculosis, and possibly HIV.<sup>225,226</sup> In fact, nosocomial transmission of *H. pylori* is the only proven mode of transmission.<sup>226</sup> According to Tytgat, the rate of iatrogenic infection may approximate 4 per 1000 endoscopies (0.4%) when the prevalence of *H. pylori* in the endoscoped population is around 60%.<sup>227</sup> He suggests that the rate of iatrogenic infection may reach 1% in areas of the world utilizing improper disinfection techniques.<sup>227</sup> The retrospective study by Langenberg et al in the Netherlands had a rate of 1.1% for *H. pylori* negative patients to develop iatrogenic infection from endoscopy when alcohol was used as the disinfectant instead of gluteraldehyde.<sup>228</sup>

Even before the “discovery” of *H. pylori*, Ramsey et al reported that 17 of 37 (45.9%) subjects participating in studies of gastric acid secretion became hypochlorhydric<sup>229</sup> (a condition that occurs during the acute phase of *H. pylori* infection following gastric biopsy<sup>230</sup>). Iatrogenic infection is also responsible for postendoscopic acute gastric mucosal lesions (sub-acute *H. pylori* infection) found in Japan that often follows endoscopy as a result of the ineffective disinfection methods utilized.<sup>194,228,230,231</sup> Proper cleaning requires use of a detergent and brushing (and often use of an enzymatic cleaner) to remove blood, mucous, and tissue from the endoscope channels prior to disinfection.<sup>225,227</sup> In 1990, the working party to the World Congresses of Gastroenterology recommended that the endoscope be soaked in 2% activated glutaraldehyde for at least 5-10 minutes, 10 minutes being sufficient to prepare the instrument for use in any patient about to undergo endoscopy.<sup>232</sup>

Rohr et al investigated the prevalence of *H. pylori* in patients attending hospitals in San Paulo, Brazil (most of which did not follow CDC endoscopy cleaning guidelines).<sup>233</sup> He found *H. pylori* positive patients to have had a greater number of prior endoscopies than *H. pylori* negative patients, although the differences were not statistically significant.<sup>233</sup> A study by Kaneko et al in Japan found that careful cleaning of the endoscope with glutaraldehyde, but not alcohol, may be sufficient to avoid iatrogenic transmission of *H. pylori* infection.<sup>234</sup> Biopsy forceps typically penetrate the gastric mucosa and are difficult to clean.<sup>227</sup> Therefore, sterilization of the forceps or preferably use of disposable forceps is essential.<sup>227</sup> Studies in Japan<sup>194</sup> and Taiwan<sup>235</sup> suggest that mechanical washing

of the endoscope is superior to manual washing in preventing iatrogenic spread of *H. pylori*, especially in situations where recommended disinfection procedures may not be routinely followed. Fantry et al, in a study in Baltimore, Maryland found that endoscopes were frequently contaminated (61% of the time) with *H. pylori* following procedures on *H. pylori* infected patients, but that risk of infection was minimal if proper disinfection methods were utilized.<sup>226</sup> A study of disinfection procedures for endoscopes in 20 Japanese hospitals found that *H. pylori* infection following endoscopy was due to inadequate disinfection procedures rather than to any resistance of *H. pylori* to disinfectants.<sup>236</sup>

## **SUMMARY OF PUBLISHED LITERATURE**

*H. pylori* is a ubiquitous bacterium with approximately 50% of the world's population estimated to be infected.<sup>237</sup> The prevalence of *H. pylori* infection varies widely by geographic area, age, race, ethnicity, and socioeconomic status. Rates appear to be higher in developing than developed countries with most of the infections occurring during childhood. *H. pylori* causes chronic gastritis and has been associated with several serious diseases of the gastrointestinal tract, including duodenal ulcer and gastric cancer. Since its "discovery" in 1982 by Warren and Marshall, *H. pylori* has been the topic of extensive research.

A number of studies have included questionnaire components that have been used to investigate factors possibly related to the etiology of *H. pylori* infection. The majority of recent studies have found no significant association with current smoking or any other measure of tobacco use. Depending upon the

population studied, alcohol consumption appears to either have no association with *H. pylori* infection or to have a slight protective effect. Adequate nutritional status, especially frequent consumption of fruits and vegetables and vitamin C, appear to protect against infection with *H. pylori* although the mechanism of action is not known. In contrast, food prepared under less than ideal conditions, or exposed to contaminated water or soil may increase risk of *H. pylori* infection. Although the evidence is still contradictory, the occupational group that appears to be at greatest risk of becoming infected with *H. pylori* is endoscopists. Since risks are not elevated for dentists, this suggests that gastric mucous may be a better medium for transmission of *H. pylori* than saliva. Drinking water source has been related to risk of *H. pylori* infection in some but not all studies. Since *H. pylori* has recently been detected in surface and shallow ground water, this is an area that deserves further investigation. Most studies have found no association between adult pet ownership and risk of *H. pylori* infection. Although several studies have suggested sheep as a possible source of *H. pylori* transmission, this hypothesis deserves additional investigation. Since only a few studies have investigated childhood exposure to animals, this also warrants further research. Overall, inadequate sanitation practices such as having no bathroom, refrigerator, or hot water supply during childhood and improper handwashing practices after using the toilet appear to be related to higher prevalence of *H. pylori* infection. All recent studies that evaluated crowding/high density living conditions using measures such as sibship size, number of persons in the home or per room, crowding index, or having to share a room or



bed with a parent, noted a positive association with prevalence of *H. pylori*. This suggests that crowded conditions may facilitate the transmission of infection among family members and is consistent with data on intrafamilial and institutional clustering of *H. pylori* infection. Low social class, whether measured by education, occupation, or income, has been consistently linked to *H. pylori* infection. Although probably not a risk factor in itself, social class represents differences in lifestyle factors that may be related to the risk of *H. pylori* infection. Only a small number of studies have evaluated the relationship between family history of gastric disease and *H. pylori* infection and the results have been inconclusive.

Understanding the route of transmission of *H. pylori* is important if public health measures to prevent the spread of *H. pylori* are to be implemented. Nosocomial transmission of *H. pylori* is the only proven mode of transmission. Difficulty in adequately disinfecting the endoscope is the major cause of iatrogenic infection in patients following endoscopy. For the general population, the most likely mode of transmission is person to person, either by the oral-oral route (through saliva or vomitus) or possibly by the fecal-oral route. The person-to-person mode of transmission is supported by the higher incidence of infection among institutionalized children and adults and the clustering of *H. pylori* infection within families. Also lending support to this concept is the detection of *H. pylori* DNA in saliva, dental plaque, gastric juice, and feces. The gold standard, isolation of *H. pylori* by culture from these sources has been performed by some investigators, but has proven to be problematic for others. Waterborne

transmission, probably due to fecal contamination, may be an important source of infection, especially in parts of the world where untreated water is common. Recent studies in the United States have linked clinical *H. pylori* infection with the consumption of *H. pylori* contaminated well water. This is an area of research worthy of further investigation. Although the principle reservoir for *H. pylori* is people, *H. pylori* has been isolated from non-human primates and domestic cats. However, even if *H. pylori* occurs naturally in non-human primates, it is unlikely to be a major route of transmission since in most of the world direct contact between humans and monkeys is limited. Although *H. pylori* has been isolated in domestic cats, additional research in this area has suggested that *H. pylori* is probably uncommon in domestic cats and thus is probably not a major concern for cat owners. The most recent reservoir suggested for *H. pylori* transmission is the housefly. However, evidence is lacking that *H. pylori* can be transmitted to humans from flies that have been in contact with *H. pylori* infected feces. Nevertheless, the hypothesis is appealing since flies are known to carry many other infectious agents. Knowledge of the epidemiology and mode of transmission of *H. pylori* are important to prevent its spread and may be useful in identifying high risk populations, especially in areas with high rates of gastric lymphoma, gastric cancer, and gastric ulcer.

## **CHAPTER III. METHODS**

### **STUDY POPULATION**

In 1989, as part of a previous epidemiologic study conducted by the National Cancer Institute (NCI) and the Beijing Institute for Cancer Research (BICR) in Linqu county, Shandong Province, China, the names of all residents aged 35-64 were transcribed from village lists in 14 villages selected at random from five townships.<sup>12</sup> The names of all individuals aged 35-39, from the same 14 villages, were added to the study roster in 1994, in preparation for a joint NCI/BICR randomized intervention trial to inhibit progression of precancerous gastric lesions. Chinese health officials visited the 4,326 individuals on the roster, explained the study, and invited their participation in a screening program that included gastroscopy, gastric biopsy, and phlebotomy.

Of the 4,326 possible participants, 210 subjects were excluded from the study because they were not medically eligible for endoscopy. Specific reasons for exclusion included: a bleeding disorder, any type of cancer, a history of liver disease, renal disease, chronic obstructive pulmonary disease, or other life-threatening illness. Also excluded from the trial were 226 subjects who refused endoscopy (afraid, felt there was no need, or couldn't tolerate the procedures) and all the eligible subjects from one village (291) because they participated in an earlier pilot study of the intervention agents. As a result, the study population for the intervention trial consisted of 3,599 subjects from 13 villages who had undergone gastroscopy, gastric biopsy, and phlebotomy.

A 5-ml blood sample was drawn from each potential study subject prior to the beginning of the trial. Serum was separated and aliquoted in the field, stored immediately at -20 degrees C, and then transferred to a -70 degrees C freezer at BICR. One aliquot of serum (0.5 ml) was tested in Beijing by Dr. Lian Zhang, BICR, for IgG antibodies to *H. pylori*. *H. pylori* strains cultured from gastric biopsies of two patients in Linqu County were used to provide the antigenic preparation for serology. The two strains were grown on blood agar plates for 48 hours and then harvested in distilled water. The cell suspensions were sonicated six times for 30 seconds each. The protein concentrations were measured by the Markwell et al. modification of the Lowry method (1978) and diluted to 10 µg/ml, and the soluble material from the two strains was pooled for an ELISA procedure.<sup>21</sup> Microtiter plates were prepared using 1 µg total protein per well. All assays were performed on coded samples in duplicate and then repeated. Each microtiter plate was read at 414 nm. Each subject was considered positive for *H. pylori* infection if the ELISA absorbance reading for IgG or IgA was 1.0 or higher, a cutoff based on examination of the distribution of readings in relation to a group of uninfected persons and reference sera. Although the sensitivity and specificity of this *H. pylori* antigen preparation derived from two Chinese strains was not determined, a similar preparation from five Chinese strains using a cut-point of 0.514 yielded a specificity of 94.9% based on 39 *H. pylori*-negative (by histology, culture, and direct urease assay) U.S. children.<sup>30</sup> The sensitivity for the five-strain antigen in 132 Chinese subjects with biopsy-confirmed *H. pylori* infection was 100%.<sup>30</sup> A somewhat lower

sensitivity and a somewhat higher specificity might be expected for the two-strain antigen and cut-point of 1.0 utilized in this study. The intra-assay and interassay variations based on positive and negative control sera were <10%.

In order to participate in the 42-month intervention trial, all study subjects had to sign an informed consent indicating their willingness to participate.

Thirty-nine subjects elected not to participate. An additional 149 subjects were excluded because they were deceased (14), were "out-of-scope" for age or village (42), had a history of allergy to antibiotics (67), or they were not tested for antibodies to *H. pylori* (26). The remaining 3411 male and female subjects from 13 villages were enrolled in the intervention trial in September, 1995. They were distributed as follows:

Village	Male	Female	Total
Xi Quan	131	116	247
Li Hu Zhuang	129	131	260
Wang Jia Zhuang	125	117	242
Xi Si Hou	63	49	112
Li Jia Gou	179	154	333
Suo Zhuang	198	200	398
Huang Ai Quad	78	90	168
Yang Jia He	127	140	267
Xin Zhuang	148	136	284
Guo Jia Zhuang	196	165	361
Hou Jia He	212	194	406
Hou He Ye	92	90	182
Nan Yang He	75	76	151
Total	1,753 (51.4%)	1,658 (48.6%)	3,411

## **DESCRIPTION OF AREA**

Shandong Province is one of the least economically developed provinces in China and Linqu County is one of the poorest counties in Shandong, with 3/4 of the land area located in mountainous regions resulting in infertile soil and periodic severe droughts. Maps showing the location of Shandong Province and Linqu County are found in Appendix 1. Linqu county has a population of about 900,000 and over 600 people die from stomach cancer each year (42% of all deaths from cancer). The annual stomach cancer mortality rates for Linqu County are 70 per 100,000 for men and 26 per 100,000 for women.

The 13 rural villages range in size from 642 to 1845 inhabitants with an average population per village of about 800. Farming is the major occupation and source of income for residents. The average annual per capita income is about \$200. Cash crops include wheat, sweet potatoes, peanuts, and apples. There is variation in the socio-economic status among the villages due to differences in the ability of the land to support farming. There is also variation in the source of water, with one village using a public well, other villages using private wells, and still others using running water piped in from a village water tower.

Most of the villages are well planned and consist of brick houses built in the last 10-15 years. Houses range from three to five rooms and have court yards which contain the families's animals (e.g., ducks, chickens, pigs). Floors are either dirt, cement, or brick. All homes have electricity, but the lighting is limited with many homes having single light bulbs hanging from the ceiling.

Although most homes have a TV set, many have ceiling fans, and a few have telephones, they lack other modern conveniences such as refrigerators, washing machines, dish washers, and air conditioners. Kitchens and pit privies/outhouses are located outside the main house. Food is stored in one room of the house. A typical meal consists of pancakes or steamed bread, some vegetables, and sometimes salty vegetables with a little meat. Villagers buy food at the village store or at the free market held every five days in the town or larger villages. All the elementary age children attend school (the larger villages have their own elementary school), but 42% of the adult residents have had no schooling. The larger villages have their own village doctor; the smaller villages share doctors. The village leader and a village committee oversee the administration of each village.

## **STUDY DESIGN**

This study is a double-blinded cross-sectional investigation of 3411 *H. pylori* infected and uninfected adults enrolled in a joint NCI/BICR randomized intervention trial to inhibit progression of precancerous gastric lesions in Linq County, Shandong Province, China. Responses to a structured questionnaire (Appendix 2) were used to evaluate factors that influence the transmission of *H. pylori* infection in this rural area of China. Sample size calculations indicated that the study should have adequate power (at least 90%) to detect a prevalence rate ratio of 1.2 or greater.

## INTERVIEW AND QUESTIONNAIRE

In-person interviews lasting approximately 15 minutes were conducted in Chinese in the homes of *H. pylori* infected and uninfected subjects by trained BICR field staff from October 1997 - May 1998. Both the interviewers and the interviewees were blinded to the *H. pylori* sero-status of the study participants. The questionnaire (Appendix 2) was designed to study risk factors for infectious disease in general and *H. pylori* in particular and to investigate potential modes of transmission. Information was collected on childhood socioeconomic factors, personal hygiene, and exposures related to food, drinking water, waste water, and animals. Topics ascertained in the questionnaire included background and demographic information (marital status, education, occupation, income), household composition (number of people, number of young children, bed sharing, animals), water and personal habits (source of drinking water; water storage; water treatment; washing of chopsticks, bowls and cups; sharing of cups; hand washing practices; bathing practices; teeth brushing), eating habits (consumption of sweet and sour pancakes and raw fruit and vegetables, whether raw fruit and vegetables are washed or peeled before eating, and presence of gastro-esophageal reflux), smoking and drinking habits (ever, age start, current status, frequency, and duration), and childhood household composition (type of floor, number of people, number of children, animals, bed sharing, premastication of food).

The questionnaire was designed by the principal investigator, CAPT Linda Morris Brown, with the assistance of scientists from BICR, NCI, and the



Uniformed Services University of the Health Sciences (USUHS). Drs. Jun-Ling Ma and Wei-dong Liu supervised the training of six Chinese interviewers and the administration of the Chinese-version questionnaire to study subjects. The 10-15 minute interview used a pre-coded structured questionnaire. The coding manual was developed by NCI and BICR. All data were keyed by a BICR coder and 100% verified by a second coder. A 10% sample of the questionnaires were mailed to NCI for verification by the principal investigator. Dr. Wei-cheng You reviewed a sample of tape-recorded interviews to check agreement with completed questionnaires.

After the data were keyed and verified they were computer edited. Range checks were developed to ensure that specific data items had acceptable codes and logic checks were developed to ensure that there was consistency between related data items. A computer disk containing the edited data was mailed to the principal investigator. Frequency distributions for all data items were produced and reviewed for inconsistencies. An analytic file was prepared by Information Management Systems, a NCI computer contractor, under the direction of the principal investigator.

Subject's current occupation was recorded verbatim. These responses were grouped into the following categories: administrative, technical/clerical/sales, precision production, operator/fabricator/laborer, service occupations, farming, and animal worker based on the Standard Occupational Classification Manual 1980 (U.S. Department of Commerce). Data on median village education level was supplied by the Chinese collaborators. These data

were used to group villages into three education level categories: high (27% had an elementary school education), medium (22% had an elementary school education), and low (15% had an elementary school education). Questionnaire data were merged with a file containing information on *H. pylori* and pathology test results and a file containing information on garlic and other allium vegetable consumption.

### **RECLASSIFICATION OF *H. PYLORI* STATUS**

For the Intervention Trial, a subject was considered seropositive if at least one of two optical density readings for IgG or one of two optical density readings for IgA was 1.0 or greater. All other subjects were considered seronegative. For the purposes of the cross-sectional study, more conservative definitions of seropositive and seronegative were employed that included the establishment of a gray or indeterminate zone of values ( $\pm 10\%$  of the cutoff value of 1.0). A subject was considered seropositive if both IgG optical density readings were 1.1 or higher and seronegative if both IgG values were 0.9 or lower and neither IgA value was 1.0 or greater. Subjects with missing IgG values were included in the gray zone.

### **DATA ANALYSIS**

Since this is a cross-sectional study, the outcome of interest is the prevalence of *H. pylori* infection as indicated by serology. The measure of association used in the standard analysis is the prevalence odds ratio. Because

the data were multinomial, (i.e., data in a discrete distribution associated with events which might have more than two outcomes - negative, positive, and indeterminate) maximum likelihood estimates were computed using polychotomous logistic regression (BMDP PR, 1990). Age, as a continuous variable, was included in all logistic models to control for potential confounding. Because subjects may share unmeasured risk factors for *H. pylori* infection with members of their families, the infection status may be correlated within families, conditional on measured covariates. Because standard calculations of variances based on the polychotomous logistic model assume that responses are independent, conditional on covariates, they can be misleading in this application. Therefore, the bootstrap based on resampling families with replacement was used to estimate variances and covariances of estimated log relative odds parameters,  $\hat{\beta}_1$  and  $\hat{\beta}_2$  which are defined precisely in equation [1] below and of functions of  $\hat{\beta}_1$  and  $\hat{\beta}_2$ . To estimate the needed variances and covariances, 100 bootstrap replicates were used.

The prevalence odds ratio may not provide a good estimate of the relative risk, because *H. pylori* positivity is common in this population (more than 60%) and thus does not meet the rare disease assumption. However, prevalence rate ratios can be calculated directly from these data because they come from a cross-sectional sample of a known population. Using predictive models, the relative odds ratio (ROR), the prevalence rate (PR), and the prevalence rate ratio

(PRR) were calculated for subjects aged 40, 50, and 60 using polychotomous logistic regression as described next.

Let  $X$  be a  $P+1$  dimensional vector of covariates and let  $\beta_1$  and  $\beta_2$  be corresponding  $(P+1) \times 1$  vectors of polychotomous logistic regression coefficients corresponding to the outcomes  $D=1$  (*H. pylori* positive) and  $D=2$  (*H. pylori* indeterminate). The vector  $X$  has 1 as its first component, corresponding to an intercept, and  $D=0$  corresponds to *H. pylori* negative. The basic polychotomous logistic model is then, for  $i=1$  or  $2$ ,

$$P(D=i|X) = \exp(\beta_i^T X) / \{1 + \exp(\beta_1^T X) + \exp(\beta_2^T X)\}, \quad [1]$$

where  $T$  indicates transposition. Suppose  $X_0$  is a reference covariate pattern, then the relative odds ratio for  $i=1$  is:

$$ROR = \{[P(D=1|X)/P(D=0|X)]/[P(D=1|X_0)/P(D=0|X_0)]\} = \exp\{\beta_1^T (X - X_0)\}. \quad [2]$$

Note that ROR does not depend on the intercept  $\beta_{10}$ , but only on the  $p$  other components of  $\beta_1$ , namely  $(\beta_{11}, \dots, \beta_{1p})^T$ . Prevalence rates of *H. pylori* infection,

$$PR = P(D=1|X)$$

are calculated directly from [1]. Prevalence rate ratios (PRRs) comparing covariate level  $X$  with the reference level are computed from [1] using

$$PRR = P(D=1|X) / P(D=1|X_0).$$

The variables used in the two main models were: Model 1 - frequency of hand washing before meals (>50% of the time, <50% of the time), number of children in the household (0-1, 2+), and median village education level (high, medium, low); Model 2 - frequency of hand washing before meals (>50% of the time, <50% of the time), number of children in the household (0-1, 2+), and

source of drinking water (deep private well, shallow private well/deep village well, shallow village well). Median village education level and source of drinking water were included in separate models because they both represented differences in *H. pylori* serostatus by village and thus were correlated. 95 % confidence intervals (CIs) were calculated from the 2.5th and 97.5th quantiles of the bootstrap distribution, based on resampling and using 1000 bootstrap replicates.

## **HUMAN SUBJECTS AND CONFIDENTIALITY**

The principal investigator received clinical exemption from the Office of Management and Budget (OMB) Clearance for the questionnaire and Institutional Review Board (IRB) approval from the BICR IRB, the Westat, Inc. IRB, the NCI IRB, and the USUHS IRB. All information obtained from the study was and will be treated as confidential. A study ID number replaced the subject's name on all documents received by NCI. The informed consent for the intervention trial included permission for the administration of a questionnaire at 12 and 24 months to collect basic information on health and lifestyle factors. The questionnaire for this study was submitted to the IRBs as an amendment to the original protocol for the Intervention Trial.

## **INVESTIGATORS**

CAPT Linda Morris Brown was responsible for the overall design, management, and data analysis for the study. Assistance in the design of the questionnaire was supplied by Drs. Jun-Ling Ma, Wei-dong Liu, and Wei-cheng

You. Primary support and management of field activities was provided by the BICR under the direction of Drs. Jun-Ling Ma and Wei-dong Liu. They were responsible for translating the questionnaire into Chinese and monitoring field support activities including the training of interviewers, interviewing subjects, and monitoring quality control measures. The questionnaire was back-translated by a Chinese translator under contract to Westat, Inc. and by Ms. Katherine Chen, a NCI employee and was found to agree with the original English version.

## CHAPTER IV. RESULTS

Interviews were completed with 3,288 (96.4%) of the 3,411 study subjects enrolled in the Shandong Intervention Trial. Reasons for non-response included death (54 subjects; 1.6%), dropped out of trial (33 subjects; 1.0%), lost to follow-up (10 subjects; 0.3%), and refusal (26 subjects; 0.8%). The *H. pylori* serostatus of the participants was positive for 1994 subjects (60.6%), negative for 1019 subjects (31.0%), and indeterminate for 275 (8.4%).

### DEMOGRAPHIC CHARACTERISTICS

Table IV-1 presents the number of subjects by *H. pylori* serostatus according to agegroup, gender, gastric pathology category, and village. The percent positive decreased with age ranging from 63% in those aged less than 40 years to 57% in those aged 55 and older. The percent positive was higher in females (63%) than males (59%). The percent positive varied greatly by gastric pathology category. Subjects with normal gastric mucosa or superficial gastritis have the lowest prevalence of *H. pylori* infection (28%); intermediate levels (46%) were seen for subjects with mild chronic atrophic gastritis (CAG); higher levels (67%-77%) were seen for subjects with other CAG, intestinal metaplasia, and dysplasia. The highest prevalence of infection was seen for subjects with cancer (80%), although this figure was based on only five subjects. There was also significant variation by village ( $\chi^2=120.76$ , d.f.=12,  $p<0.001$ ). The highest

rate (76%) was seen among subjects from Wang Jia Zhuang, whereas the lowest rate (47%) was seen among subjects from Guo Jia Zhuang.

All analyses were run using polychotomous logistic regression. Since results from the indeterminate group have no clear meaning, the only results reported are for *H. pylori* positive compared to *H. pylori* negative subjects. All results were adjusted for age as a continuous variable. Other variables such as village and village education status were not found to be significant confounders or effect modifiers, and thus were not included in the logistic regression models. Presented for each variable is the prevalence odds ratio (OR), the 95% confidence interval (CI) computed directly from the polychotomous logistic regression, and the bootstrap 95% CI that allows for additive familial correlation.

## **RISK FACTORS**

### **Cigarette Smoking**

Table IV-2 presents prevalence ORs for *H. pylori* infection and smoking-related factors. The odds of ever smoking cigarettes was slightly lower for *H. pylori* positive subjects (OR=0.9, 95%CI=0.7-1.0), however, there were no consistent trends according to the age first started smoking, the number of cigarettes smoked per day, the number of years smoked, or the lifetime number of packs smoked. In addition, the OR for past smoking was slightly lower than the ORs for current smokers (0.8 vs. 0.9), but the difference was not significant.



### **Alcoholic beverage consumption**

Prevalence ORs for the association between *H. pylori* infection and alcoholic beverage consumption are presented in Table IV-3. In these data, there was no association between infection status and alcohol use overall or with any measure of alcohol consumption including age first started drinking, number of times drank per week, or with number of years drank. Among drinkers, the odds of being *H. pylori* positive was slightly reduced for current smokers (OR=0.9) and slightly elevated for past smokers (OR=1.2), although both sets of confidence intervals included 1.0.

### **Dietary factors**

Associations between the prevalence of *H. pylori* infection and dietary factors are presented in Table IV-4. There was a pattern of decreasing ORs with increasing consumption of allium vegetables (ranging from 1.0 for less than 11 jin per year to 0.8 for greater than 21 jin per year; 1 jin ~ 500 grams), although the trend was not significant ( $p$  for trend=0.50). The gradients in the ORs for the individual types of allium vegetables (garlic, garlic stalk, scallions, and chives) were less consistent. There was no apparent association between *H. pylori* infection and the number of times per month raw fruits and vegetables were eaten. ORs were reduced the less frequent raw fruits and vegetables were washed, reaching OR=0.7 (95%CI=0.5-0.9) for subjects who never washed their raw fruit and vegetables. No association was seen with the frequency that subjects peeled their raw fruits and vegetables before eating. The number of

sour or fermented pancakes eaten per year was associated with a slightly elevated OR, reaching 1.2 (95%CI=0.8-1.7) in the highest consumption category; whereas the number of sweet or nonfermented pancakes eaten per year was associated with a reduced OR (OR=0.8, 95%CI=0.7-0.9). The OR was only slightly elevated (OR=1.1) for subjects who preferred their food moderately or very salty.

### **Occupation**

Table IV-5 presents ORs for the association between the prevalence of *H. pylori* infection and various occupations. The majority of subjects (75.5% of those *H. pylori* positive and 75% of those *H. pylori* negative) reported having an occupation as a farmer. Although none of the ORs were statistically different from 1.0, elevated ORs were associated with employment in precision production and service occupations; reduced ORs were associated with employment in technical/clerical/sales, operator/fabricator/laborer, and as animal workers.

### **Water-related exposures**

Presented in Table IV-6 are ORs for the prevalence of *H. pylori* infection and its relationship with water-related exposures. Source of drinking water was found to vary between *H. pylori* positive and negative subjects. Compared to subjects who obtained their drinking water from deep private wells, ORs were significantly elevated for subjects who obtained their water from a shallow village well (OR=1.8, 95%CI=1.4-2.3). ORs were also elevated for subjects who used a

shallow private well (OR=1.3), a deep village well (OR=1.4), and running/spring water (OR=1.4). A reduced OR was seen for subjects who obtained their drinking water from a pond/river/ditch (OR=0.8), but the majority of those subjects had obtained their drinking water from a river. Three *H. pylori* positive subjects and one *H. pylori* negative subject reported obtaining their drinking water from a pond or ditch. Similarly, a greater percentage of *H. pylori* positive subjects reported washing diapers in a pond or ditch (OR=2.2, 95%CI=0.6-7.8). There was a slight decrease in the ORs associated with increased number of days that drinking water was stored in a jar, ranging from 1.0 for 0, 0.9 for 1 or 2, and 0.8 for 3 or more; however, all CIs overlapped. There appeared to be no protective effect of boiling drinking water.

An elevated OR was associated with washing or bathing when the weather was warm (OR=1.3, 95%CI=1.0-1.6). The highest ORs were seen for subjects who bathed in a pond or ditch (OR=1.6, 95%CI=1.0-2.4) or who bathed at a public bathhouse (OR=2.8, 95%CI=0.9-8.4). However, there did not appear to be a consistent trend with the number of times bathed when warm. The OR for washing or bathing when the weather was cold was only slightly elevated (OR=1.1). Overall there was no association between *H. pylori* infection and swimming in a river or reservoir, however, the OR was slightly elevated (OR=1.2) for subjects who reported swimming in a river or reservoir more than four times per year.

## **Exposure to animals and pets**

Presented in Table IV-7 are ORs for the association between the prevalence of *H. pylori* infection and exposure to pets and other domestic animals. ORs were reduced for keeping any animal in the house as an adult (OR=0.7, 95%CI=0.5-1.0), and significantly reduced for keeping only one animal in the house as an adult (OR=0.5, 95%CI=0.3-0.9). ORs were reduced for keeping cats (OR=0.6, 95%CI=0.3-1.1) or rabbits (OR=0.7, 95%CI=0.4-1.1), but not dogs (OR=1.2, CI=0.3-4.5). There was also a modest reduction in the OR associated with keeping any animal in their courtyard as an adult (OR=0.8, 95%CI=0.5-1.2). ORs were reduced for all 11 types of animals studied that were kept in the courtyard, including cats (OR=0.7), dogs (OR=0.9), and sheep (OR=0.3).

Overall, there was no association between *H. pylori* infection and keeping animals in the house when the subject was ten years old. However, the ORs associated with keeping cats (OR=0.7, 95%CI=0.5-1.0) or dogs (OR=0.5, 95%CI=0.3-1.0) in the house when the subject was ten years old were reduced. The OR also was not elevated for subjects who had a job working with animals (OR=0.5, 95%CI=0.2-1.2).

## **Sanitation/hygiene factors**

ORs for the association between the prevalence of *H. pylori* infection and certain sanitation or hygiene factors are presented in Table IV-8. The OR associated with spitting onto the ground was slightly reduced (OR=0.9, 95%CI=0.8-1.0), but no gradient was evident for the number of times per month that subjects spit onto the ground. There was also no association with the number of times per month that subjects brushed their teeth. The OR was elevated for subjects who reported washing their hands before eating less than half the time (OR=1.6, 95%CI=1.0-2.5) or never (OR=3.8, 95%CI=0.5-31.0). On the other hand, reduced ORs were seen for subjects who did not always wash their hands after bowel movements and for subjects who never washed their hands before preparing meals. No consistent patterns were seen with frequency of washing hands or body with soap, frequency of cup washing after use, the temperature of the water used to wash chopsticks and bowls, or frequency of pre-chewing their child's food. Most subjects always washed their chopsticks and bowls after eating, but few always washed them with detergent. The ORs were reduced for subjects who shared cups with their family less than half the time, for subjects who never kissed young children on the lips or who were never kissed as children by their parents on the lips, and for subjects whose house where they lived when they were ten years old had a floor of some material other than dirt.

#### **Density/crowding factors**

Presented in Table IV-9 are the prevalence ORs for the association between *H. pylori* infection and density/crowding factors. As an adult, there was no consistent association with total number of people in the household and the OR was only slightly elevated for sharing a bed with a spouse (OR=1.1, 95%CI=0.9-1.4). However, the ORs were elevated for more than one child in the household (OR=2.0, 95%CI=1.0-3.7), sharing a bed with more than two people (OR=2.1, 95%CI=1.1-3.8), and sharing a bed with more than one child (OR=1.7, 95%CI=1.0-2.8). On the other hand, the ORs were less than 1.0 for density factors when the subject was 5 or 10 years old such as number of people in the household and number of people shared a bed with.

### **Social factors**

The association between social factors and prevalence of *H. pylori* infection is presented in Table IV-10. The most striking finding was with village education level; the OR increased with decreasing village education level, from 1.0 for high, to 1.7 (95%CI=1.4-2.1) for medium, to 2.4 (95%CI=2.0-3.0) for low ( $p$  for trend<0.001). No consistent patterns were seen for socioeconomic variables at the individual level (e.g., subject's education level, spouse's education level, or subject's annual income). The ORs were reduced for subjects who were divorced or never married (OR=0.4) compared with those who were married, but the number of subjects in those categories was small.

### **Gastric factors**

The association between the prevalence of *H. pylori* infection and gastric factors is presented in Table IV-11. Overall, there was no association between ever having gastric reflux and prevalence of *H. pylori* infection. However, the ORs were slightly reduced for subjects who had reflux 4-8.9 (OR=0.9) and nine or more (OR=0.8) times per month.

## **MULTI-VARIATE ANALYSIS**

Presented in Table IV-12 are the prevalence rates (PRs), prevalence rate ratios (PRRs) and relative odds ratios (RORs) for combinations of models according to age (40, 50, or 60), percent of time washed hands before eating (<50% or >50%), number of children in the household (0-1 or 2+), and village education level (low, medium, or high). Within each age category, the referent group is subjects who washed their hands >50% of the time, who had 0-1 children in their household, and who came from a village with high education level. The RORs are the same for each age category because the parameter estimate for age when two groups being compared have the same age, drops out.

There were only small variations in the PR by age, with the highest PR seen for subjects aged 40 and the lowest for subjects aged 60. For example, the PR for a subject aged 40 who washed their hands <50% of the time, had 2+ children in their household, and came from a low education village was 74%; the PR for a 60 year old person with the same factors was 71%. Within each age category, the PR was highest for those subjects from a low education village with

at least one other risk factor (i.e., washed hands <50% of the time or had 2+ children in the household). The lowest PR for each age category (51% for age 40, 48% for age 50, and 46% for age 60) was for subjects with none of the risk factors (i.e., they washed their hands >50% of the time and had fewer than 2 children in their household) who lived in a high education village. Within age categories, PR was strongly related to village education level, with the highest PRs seen for subjects who lived in low education villages, intermediate values for subjects who lived in medium education villages, and the lowest PRs seen for subjects who lived in villages with the highest education level.

The PRRs varied little by age. Most of the PRRs were statistically different from 1.0, ranging from 1.0 to 1.5. Because the background rate of *H. pylori* is high in this population, even a small PPR has a big impact. An inverse relationship between prevalence of *H. pylori* infection and village education level was apparent, with the subjects who lived in the lowest education villages having the largest PRRs and subjects who lived in the highest education villages the smallest. In general, PRRs were lowest for subjects who washed their hands <50% of the time and who had 2 or more children in their household.

Unlike the PRRs, the RORs showed great variation both within and among village education categories. Within a village education category the greatest RORs was seen for subjects with both risk factors (washed hands <50%, had 2+ children); the lowest was seen for subjects with neither risk factor (washed hands >50%, had 0-1 children. For example, among subjects who lived in villages with low education the RORs ranged from 8.6 for subjects who had



both risk factors, 5.0 or 4.1 for subjects who had one risk factor, and 2.4 for subjects who had neither risk factor. The RORs also varied greatly by village education level. The RORs ranged from 8.6 (95%CI=3.9-22.2) for subjects with both risk factors who lived in a village with the lowest education level, to 6.0 (95%CI=2.7-16.2) for subjects who lived in a village with an intermediate education level, to 3.6 (95%CI=1.6-9.3) for subjects who lived in a village with the highest education level.

Presented in Table IV-13 are the PRs, PRRs and RORs for combinations of models according to age (40, 50, or 60), percent of time washed hands before eating (<50% or >50%), number of children in the household (0-1 or 2+), and source of drinking water (shallow village well, shallow private well or deep private well, and deep private well. Within each age category, the referent group for the PRRs and RORs is subjects who washed their hands >50% of the time, who had 0-1 children in their household, and who had a deep private well.

The PRs, PRRs, and RORs followed similar patterns to those seen in Table IV-12, but the values were lower for each combination of variables. Overall, the PRs, PRRs, and RORs were highest for subjects who obtained their drinking water from a shallow village well, intermediate for subjects whose drinking water came from a shallow private well or a deep village well, and lowest for those who obtained their drinking water from a deep private well. For example, the PRs ranged from 73% (95%CI=63-81%) for subjects aged 40 who washed <50% of the time, had less than two children, and obtained their drinking water from a shallow village well to 49% (95%CI=43-55%) for subjects aged 60

who washed >50% of the time, had less than two children, and obtained their drinking water from a deep private well. The PRRs ranged from 1.0-1.4. The RORs also showed variation by source of drinking water. The RORs ranged from 7.0 (95%CI=3.4-17.6) for subjects with both risk factors whose drinking water came from a shallow village well, to 4.9 (95%CI=2.3-12.2) for subjects whose drinking water came from a shallow private well or a deep village well, to 3.9 (95%CI=1.9-9.4) for subjects whose drinking water came from a shallow village well.

## CHAPTER V. DISCUSSION

This large cross-sectional study conducted among adults living in 13 villages in Shandong Province, China provided the opportunity to assess risk factors related to the prevalence of *H. pylori* infection. Factors of particular interest included measures of adult and childhood socioeconomic status, source of drinking water, personal hygiene and sanitation factors, sharing of utensils, potential food contamination, and exposure to animals.

### RESEARCH QUESTION 1:

*Is there an association between H. pylori positivity and drinking water source (i.e., shallow well, deep well, pond, river, ditch, or running water), storage, or treatment?*

There is some suggestion in the data, that source of drinking water is potentially related to *H. pylori* infection. Compared with subjects who obtained their drinking water from deep private wells, ORs were elevated for subjects who obtained their water from wells that were more apt to be contaminated with fecal or other material containing *H. pylori* (shallow private wells (OR=1.3), deep village wells (OR=1.4), or shallow village wells (OR=1.8)). The possible role of waterborne transmission of *H. pylori* is supported by a study in the U.S. that reported a strong association between consumption of well water contaminated by *H. pylori* and *H. pylori* positive status in persons consuming the water.<sup>212</sup> The finding of *H. pylori* DNA in the drinking water in Peru suggests that waterborne

transmission may be important in areas of the world, such as Peru and China with untreated water. Klein et al found that the water supply in Lima, Peru may be vulnerable to bacterial contamination, especially when it is stored in a cistern;<sup>144</sup> however, this study detected a slight protective effect for subjects who stored their water in a jar for more than three days. Although it has been shown that *H. pylori* can live for several days in tap water in its infectious bacillary form,<sup>205</sup> longer storage may have resulted in the conversion of *H. pylori* into its coccoid form.<sup>203</sup> Surprisingly, in this study there was no evidence of a protective effect of always boiling water before drinking it. Although the data from this study are not totally consistent, the elevated ORs for some sources of drinking water suggest that the high prevalence of *H. pylori* infection in this study area might be related to the presence of *H. pylori* in the drinking water.

## RESEARCH QUESTION 2:

*Is there an association between H. pylori positivity and adult sanitation and hygiene (e.g., hand washing, use of soap, bathing, teeth brushing, and sharing of cups)?*

Several studies have reported an association between poor hygiene practices and *H. pylori* infection; however, most were either conducted among children<sup>122,150</sup> or asked about childhood exposures.<sup>73,93</sup> The questionnaire for this study sought information about the frequency as an adult of hand washing before eating meals, after bowel movements, and before preparing meals. The most consistent finding was for subjects who washed their hands before eating

meals less than half the time (OR=1.6) or never (OR=3.8). There was no protective effect of washing hands, body, or chopsticks and bowls with soap or detergent. Although the majority of subjects reported always sharing cups with their family, there was a protective effect for subjects who shared cups less than half the time. These findings were in contrast to those by Peach et al in Australia<sup>62</sup> who found an elevated risk for adult subjects who did not usually wash their hands after going to the toilet (OR=4.1), but no association with frequency of sharing cups or washing hands before eating. In this study, ORs were slightly reduced for subjects who never kissed young children on the lips, whereas no association with either frequency of teeth brushing or spitting onto the ground was apparent. Several studies found the prevalence of *H. pylori* infection to be higher in subjects who did not have a bathroom, indoor toilet, or running water;<sup>73,78,93</sup> modern necessities not found in any of the homes of the study subjects. Since all of the rural Chinese study subjects ate with chopsticks, it was not possible to confirm the elevated OR of 2.5 reported among Chinese immigrants in Australia who used chopsticks. In this study, there was a borderline association for subjects who bathed when the weather was warm (OR=1.3) that reached 1.6 for subjects who washed in a pond or ditch. However, there was no gradient in risk with the number of times per month that the subject bathed. There was a slight (OR=1.2) non-significant risk for subjects who swam in a river or reservoir four or more times per year. Higher prevalence of *H. pylori* infection has been linked to swimming in a stream in Colombia,<sup>122</sup> but not to swimming near contaminated beaches or bathing in local rivers, irrigation

ditches, or lakes in Chile.<sup>125</sup> These data suggest that hand washing before meals and elimination of familial cup sharing may be important health measures to reduce the prevalence of *H. pylori* infection in China. Also, source of water used for bathing, especially pond or ditch water, may be related to increased prevalence of *H. pylori* infection.

### **RESEARCH QUESTION 3:**

*Is there an association between H. pylori positivity and social class factors?*

Social class factors (i.e., SES-based occupation, education, income, SES) have been associated with *H. pylori* infection status in a number of studies throughout the world.<sup>48,49,54,57,59-63,66,68,72,74,77-80,84,85,88,93,124,125,147,153</sup> This study noted a strong inverse relationship between village education level and prevalence of *H. pylori* infection, that reached 2.4 for those in the lowest compared to the highest village education category. However, there were no consistent associations in this study with individual measures of social class including number of years of education (subject or spouse), and subject's annual family income. These data suggest that density factors and group SES factors may be associated with the prevalence of *H. pylori* infection in rural China. The absence of an association between *H. pylori* and individual social class factors may result from a lack of heterogeneity in the study population.

#### RESEARCH QUESTION 4:

*Is there an association between *H. pylori* positivity and use of tobacco or alcohol products?*

Similar to some,<sup>13,54,63-65,68,75,87,88,92,116</sup> but not all<sup>57,61,109,112-114</sup> recent studies, this study found no significant association with current smoking or any other measure of cigarette use including age first started smoking, number smoked per day, number of years smoked, and lifetime packs smoked. All of the recent epidemiologic studies that looked at the relation between alcohol use and *H. pylori* infection reported either no association<sup>54,61-63,68,92</sup> or a reduction in risk,<sup>57,109,115,117,118</sup> that was stronger for wine than beer and more apparent at moderate to high levels of alcoholic beverage consumption. Similarly, this study found no association between *H. pylori* infection and ever/never use of alcohol, and only a slight (OR=0.9) nonsignificant reduction in the OR for subjects who drank alcohol seven or more times per week. The relative homogeneity among drinkers in this study including the lack of heavy drinkers may have limited the ability to detect a protective effect from alcohol even if it has antimicrobial properties.<sup>120</sup> These findings suggest that neither smoking nor drinking are related to the prevalence of *H. pylori* infection in this population.

#### RESEARCH QUESTION 5:

*Is there an association between *H. pylori* positivity and presence of gastro-esophageal reflux?*

Some studies have suggested that *H. pylori* infection, which may diminish acid secretion, appears to be lower in persons with gastroesophageal reflux disease (GERD).<sup>46,47</sup> GERD, the major risk factor for Barrett's esophagus, is associated with adenocarcinoma of the esophagus.<sup>46,47</sup> In this study, there were slight nonsignificant protective effects for subjects who reported the occurrence of gastric reflux 4-8.9 (OR=0.9) and nine or more (OR=0.8) times per month. These results suggest that *H. pylori* infection in Linqu county may be associated with a decreased prevalence or severity of GERD.

#### **RESEARCH QUESTION 6:**

*Is there an association between H. pylori positivity and raw fruit and vegetable consumption or preparation (i.e. washing or peeling)?*

Increased consumption of allium vegetables has been suggested as a protective factor for stomach cancer<sup>238,239</sup> and garlic has been shown to inhibit *H. pylori* in vitro,<sup>240,241</sup> but not in vivo.<sup>242</sup> In this study, there was a pattern of decreasing ORs with increased consumption of all allium vegetables combined, but the pattern was less consistent for each individual type of allium vegetable (garlic, garlic stalk, scallions, chives). Several studies have reported significantly reduced ORs and negative gradients in risk of *H. pylori* infection with increased consumption of fruits and/or vegetables, vitamin C, and beta-carotene.<sup>109,121-123</sup> In contrast, consumption of raw/uncooked vegetables was associated with elevated risk of *H. pylori* infection.<sup>122,125</sup> In these data, there was no apparent association between *H. pylori* infection and the number of times per month raw fruits and



vegetables were eaten or with the frequency that subjects peeled their raw fruits and vegetables before eating. ORs were reduced the less frequently raw fruits and vegetables were washed.

These data do not support a role for raw fruit and vegetable consumption in the prevalence of *H. pylori* infection in this study population, except for a possible protective effect of heavy intake of garlic and other allium vegetables. The reduced ORs for subjects who washed their fruit or vegetables infrequently suggests the possibility of transmission of *H. pylori* to raw fruits and vegetables via water, but not soil.

#### **RESEARCH QUESTION 7:**

*Is there an association between H. pylori positivity and adult exposure to pets and other domestic animals?*

Although *H. pylori* has been isolated from laboratory domestic cats,<sup>215,216</sup> no evidence of *H. pylori* infection was found in an investigation of stray cats.<sup>219</sup> Similarly, the epidemiologic literature suggests that adult ownership of a cat or other pet is not associated with a higher prevalence of *H. pylori* infection.<sup>62,78,80,97,148</sup> In fact, one study in the U.S. found pet owners to have significantly lower rates of *H. pylori* infection.<sup>80</sup> In this study, ORs were reduced for adults who kept cats (OR=0.6) or any animal (OR=0.7) in the house or any animal in the courtyard (OR=0.8). ORs were reduced for all types of animals that were kept in the study subject's courtyard, including cats (OR=0.7) and sheep (OR=0.3, although based on very small numbers). Exposure to sheep was

implicated in a recent study that found a high prevalence of *H. pylori* infection among Sardinian shepherds occupationally exposed to sheep.<sup>149</sup> In agreement with studies in Australia and Germany that reported no association with occupational handling of animals,<sup>62,85</sup> the OR in this study was not elevated for subjects who had a job working with animals. Thus, these data for rural China support epidemiologic studies in other parts of the world that found ownership of a cat or other domestic animal not to be associated with increased prevalence of *H. pylori* infection.

#### **RESEARCH QUESTION 8:**

*Is there an association between *H. pylori* positivity and childhood exposures (e.g. domestic animals, crowding, and eating premasticated food)?*

Although most studies found no association between *H. pylori* infection and having a pet during childhood,<sup>93,127,147</sup> several studies did report a positive association with cat ownership as a child<sup>85,146,220</sup> A study from rural Columbia found higher *H. pylori* prevalence among children who played with sheep.<sup>149</sup> In this study, there was no association between *H. pylori* infection and presence of cats (OR=0.7) or any animal (OR=1.0) in the household when the subject was ten years old. No information was sought on childhood exposure to sheep or other farm animals.

In these data, there was no indication that crowding or density factors as a child (e.g., number of people in the household when the subject was ten year old, the number of young siblings (< five years old, < ten years old) when the

subject was ten, the number of people the subject shared a bed with at ages five and ten) was related to a higher prevalence of *H. pylori* infection as an adult. This is in contrast to many recent studies that found that some measure of high density during childhood such as sibship size,<sup>67,87,93,243</sup> number of persons or children in the home,<sup>49,62,122</sup> number of persons per room,<sup>73,78,100,150</sup> or having to share a room or bed with a parent<sup>85,154</sup> was associated with prevalence of *H. pylori* infection.

According to the literature, poor hygiene or sanitation practices, especially during childhood such as having no bathroom, refrigerator, or hot water supply in the house,<sup>73,93,100,150</sup> sharing cups and having a mother who didn't use soap when she washed her hands or a mother who prechewed their food when they were a child<sup>122,151</sup> was associated with a higher prevalence of *H. pylori* infection. This study was unable to evaluate some of these factors because no subject had a bathroom, refrigerator, or hot water supply in the house as a child. The ORs were slightly reduced for subjects who were never kissed as children by their parents on the lips and for subjects whose house where they lived when they were ten years old had a floor of some material (brick, wood, cement) other than dirt. The OR was also reduced for subjects who reported that their parents never pre-chewed their food as a child, but the association was not consistent across exposure categories. These findings suggest that childhood exposures, as recalled during adulthood, are not important predictors of adult prevalence of *H. pylori* infection in this study population.

## STRENGTHS OF THE STUDY

This cross-sectional investigation allowed the opportunity to evaluate some possible etiologic factors that influence the prevalence of *H. pylori* infection in Shandong Province, China. The benefit of a cross-sectional study over a case-control study is that it is based on a sample of the general population, thus both ORs and PRRs can be calculated. An additional benefit of a cross-sectional study over a cohort study is that it can be carried out over a relatively short time period.

Bias, or a systematic error in the risk estimates due to a flaw in the design or conduct of a study, is always of concern in epidemiologic studies. Non-response bias can be a problem if the response rates are low since people who don't respond are generally not a representative group of study subjects and thus may have a different risk profile than responders. This type of bias was not of great concern in this study because of the high (over 96%) participation rates. Selection bias may occur if the way in which infected and noninfected subjects were selected induced an apparent, but not true, association with an exposure. *H. pylori* status was determined using a serologic test. For the Intervention Trial, a subject was considered seropositive if at least one of two optical density readings for IgG or one of two optical density readings for IgA was 1.0 or greater. All other subjects were considered seronegative. To improve sensitivity and specificity for the cross-sectional study, a more conservative definition based primarily on IgG values that included the establishment of a gray or indeterminate zone ( $\pm 10\%$  of the cutoff value of 1.0) was utilized. The

classification of *H. pylori* serostatus was determined scientifically based on the Elisa optical density test results. Because study investigators were blinded to the *H. pylori* serostatus of study subjects, selection bias is unlikely to have played a role in the results.

The quality of the information collected was comparable between *H. pylori* positive and *H. pylori* negative subjects (information bias). The same structured questionnaire was administered to all study subjects in person by trained interviewers. *H. pylori* is generally asymptomatic so subjects and interviewers were unaware of infection status. In addition, a survey research company, Westat, Inc. was responsible for assigning ID numbers and determining the randomization for the intervention trial; none of the NCI or BICR investigators were aware of the treatment status of participants. Thus, neither recall bias (differential memory on the part of diseased subjects in an attempt to explain their disease) nor interviewer bias (occurs when interviewers are aware of the disease status of subjects and are not objective in their interviewing techniques) could have played a role in this study. Bootstrap confidence intervals were calculated to avoid underestimation of the standard errors due to intrafamilial correlations. This did not appear to be a problem, however, as both the bootstrap and regular confidence intervals were similar. Although there may be some degree of misclassification or inaccuracies in the data acquisition, because of the reasons stated above, inaccuracies are not likely to differ systematically (differential misclassification) according to *H. pylori* serostatus.

## LIMITATIONS OF THE STUDY

There are also several limitations of this study. Similar to all cross-sectional studies, the outcome and the exposure are assessed simultaneously so it is often difficult to separate cause and effect. Also, the outcome is measured as prevalence rather than incidence of disease and will reflect *H. pylori* infections that could have occurred from early childhood to several weeks before the blood sample was drawn.

Because this study assessed the effects of many factors related to prevalence of *H. pylori* infection in other populations, it is surprising that more significant associations were not found. Non-differential misclassification (an error in the data that is not related to disease or exposure status), may have hampered the ability to detect actual associations. A lack of heterogeneity in this rural Chinese population may have limited the ability to detect differences between *H. pylori* positive and negative subjects since it is not possible to detect any causes of disease that are ubiquitous or relatively invariant within the population under study.<sup>244</sup> Not only is this a potential problem for adult exposures, but it is even more likely that subjects would have shared common environmental factors before the cultural revolution; factors that may have influenced their acquisition of *H. pylori* infection during childhood. It is also possible that almost everyone was exposed to the *H. pylori* organism during childhood and it was differences in host factors and host susceptibility that determined who became clinically infected.

Another reason for the lack of significant findings may be a result of non-differential misclassification. In this study, many questions did not seek quantitative responses so it may have been difficult for study subjects to fit their answers into the qualitative categories of “Always, Sometimes, Never”.

Answering quantitative questions also may have been difficult for the study subjects with little, if any, formal education. In addition, recall of information from childhood may have been difficult and fraught with error. For binary exposures and for continuous variables when the error was independent of the true value, any bias introduced by non-differential misclassification would have shifted the risk estimate toward the null.<sup>245</sup> Thus, the observed ORs are probably closer to 1.0 than they would have been if there were no errors in the data. Because errors are unlikely to be independent of true values in self-reported questionnaire data, when the exposure variable was polytomous (i.e., more than two categories) the bias from non-differential misclassification could be strong enough to either exaggerate or reverse the estimate of the effect of a trend.<sup>245</sup>

Because of the problem of multiple comparisons, the possibility that some of the positive findings in this study were due to chance can't be ruled out. Based on an alpha level of 0.05 five significant findings for every 100 ORs or PRRs calculated would be expected. Thus, it is important to consider the strength and consistency of the association and biologic plausibility when deciding which exposure factors may be causally related to prevalence of infection.

In the multivariate analyses there were notable discrepancies in the magnitude of the associations between the RORs and the PRRs. In these data the ROR may not have been a good estimator of the PRR because the outcome of interest was not rare in the study population. Also, because the model was based on polychotomous logistic regression, the estimates for the RORs and PRRs were based on different denominator data. The RORs compared the prevalence of exposure in persons who were *H. pylori* positive to the prevalence of exposure in persons who were *H. pylori* negative. As a result, persons with indeterminate serostatus were excluded from this analysis. The PRR compared the prevalence of being *H. pylori* positive (relative to the whole population which included persons with indeterminate serostatus) in persons with the exposure to the prevalence of being *H. pylori* positive in persons without the exposure.

## CONCLUSIONS

In summary, this study found elevated ORs for group, but not for individual social class factors. Determinants of density or crowding during adulthood, but not during childhood appeared to be related to the prevalence of *H. pylori* infection. Source of drinking water or bathing water may be associated with *H. pylori* serostatus. Use of alcohol, tobacco, raw fruits and vegetables (with the possible exception of allium vegetables) and exposure to animals during adulthood or childhood were not associated with increased prevalence of *H. pylori* infection in this rural Chinese population.



Based on the findings for the density and hygiene factors, as well as data from another study in the area that found a higher prevalence of *H. pylori* infection in the children of infected parents,<sup>103</sup> person-to-person transmission appears to be a likely route of infection in these rural Chinese villages. However, the data are not sufficient to determine whether the route was oral-oral, fecal-oral, or gastro-oral. A plausible role of waterborne transmission in this population was suggested by the possible association between *H. pylori* infection and source of drinking water and bathing water. However, a role for zoonotic transmission in the spread of *H. pylori* infection in the study area appears unlikely.

## **FUTURE DIRECTIONS**

### **Global issues**

Infection with *H. pylori* is generally asymptomatic, thus it may be well-adapted to exist in the human stomach for the lifetime of its host. Because only a small percentage of those infected develop severe disease (duodenal ulcer, gastric ulcer, gastric lymphoma, or gastric cancer)<sup>5,7,57</sup> and *H. pylori* may be protective against other conditions such as adenocarcinoma of the esophagus,<sup>46,47</sup> the public health response is not clear.

Possible questions that may require addressing include the following:

- (1) Because *H. pylori* is an organism thought to be indigenous to the human population, should it be eliminated? If yes, what is the role of public health

in discovering the route(s) of transmission, educating the public, and reducing or eliminating spread?

- (2) Should populations be screened for *H. pylori* infection? If yes, should all populations be screened or only those at high risk of gastric lymphoma or gastric cancer?
- (3) Should *H. pylori* be eliminated in all persons in whom it is detected or only in those with severe symptoms or at high risk of gastric lymphoma or gastric cancer?
- (4) Does elimination of *H. pylori* in middle-aged adults protect against the development of gastric cancer?
- (5) Should a vaccine against *H. pylori* be used, and if so, who should be vaccinated? Should its use be universal or restricted to children living in populations at high risk of stomach cancer like parts of rural China?

### **Studies within the intervention trial cohort**

To further investigate waterborne factors as a possible transmission mechanism for *H. pylori* infection in Shandong Province, I plan to conduct a small nested case-control study in collaboration with investigators from Pennsylvania State University. To evaluate whether an association exists between *H. pylori*-infected drinking water and *H. pylori* serostatus, the drinking water sources of approximately 50 *H. pylori* positive and 50 *H. pylori* negative households would be tested for the presence of *H. pylori* and compared with the serostatus of household members.

As part of the Intervention Trial, blood was drawn and *H. pylori* serostatus determined on all trial participants annually from 1996-1999. To further investigate risk factors related to the prevalence of *H. pylori* infection, questionnaire responses among subjects randomized to the *H. pylori* treatment arm whose disease has remained eradicated, who seroconverted after their infection was considered to be eradicated, and whose infection was never successfully eradicated could be compared.

### **Public health significance of *H. pylori* research in Linqu County**

This study confirmed the high prevalence of *H. pylori* infection among residents of Linqu County. In addition, it identified factors that may reduce *H. pylori* prevalence in rural China (i.e., hand washing, and higher village SES-associated factors) and others that may increase *H. pylori* prevalence (i.e., “contaminated” water used for drinking, bathing, and washing of fruits and vegetables eaten raw). Knowledge of *H. pylori* etiology and transmission are fundamental to devising approaches for controlling this infectious disease. Improvements such as increased personal and family hygiene; overall economic development, including refrigeration and better sanitation; and treatment of the water supply may have a large impact on public health in rural China.

Its parent study, a randomized intervention trial involving treatment of *H. pylori* in persons at various pathologic stages in the progression toward gastric cancer, should have a global impact by helping determine the efficacy of *H. pylori* eradication in adults at different points in this continuum. If treatment

proves successful, then routine screening for *H. pylori* and subsequent treatment may be a viable option in affluent countries with access to preventive medical services. However screening and treatment may not be efficacious in developing countries with large numbers of affected individuals. The high cost and technical difficulties involved in administering effective treatment programs may be prohibitive. In these countries, vaccination (once developed and tested) may be a better alternative. Because chronic gastritis and other gastric cancer precursors are common; *H. pylori* rates are high in children (50% at ages 3-4) as well as adults; use of antibiotics is low; and the population is well characterized, cooperative, and homogeneous, Linqu County may be an ideal location to conduct a placebo-controlled *H. pylori* vaccine trial among infants or very young children.

## TABLES

**Table II-1. Prevalence of *Helicobacter pylori* in various adult populations**

Author, Year, Ref No.	Country	No. in study	Population	Age range	Diagnostic Test	Rate
Alaganantham, 1999 <sup>35</sup>	India	354	General upper class population	12-70+	Serology	49.4%
Kimura, 1999 <sup>89</sup>	Japan	196	Institutionalized	3-64	Serology	81.1%
Wong, 1999 <sup>71</sup>	China Hong Kong Changle	397 1456	Healthy volunteers	36-65	Serology	80.4% 58.4%
Buckley, 1998 <sup>72</sup>	Ireland	1000	Blood donors	18-60	Serology	43.0%
Kawasaki, 1998 <sup>86</sup>	Nepal	1142	General population	4-93	Serology	56.8%
Kikuchi, 1998 <sup>47</sup>	Japan	4361	Public service workers	19-69	Serology	30.5%
Lin, 1998 <sup>37</sup>	Australia	273	General population	20-80	Serology	38.0%
Luzza, 1998 <sup>83</sup>	Rural Italy	705	Out-patients	1-87	Serology	63.0%
Rothenbacher, 1998 <sup>85</sup>	Germany	337	Adult students	50-85	UBT	34.8%
Senra-Varela, 1998 <sup>88</sup>	Spain	332	General population	Adult	Serology	43.0%
Souto, 1998 <sup>89</sup>	Brazil	164	General population	20-90	Serology	84.7%
Strachan, 1998 <sup>41</sup>	South Wales	1796	General population	45-59	Serology	70.0%
Stroffolini, 1998 <sup>16</sup>	Italy	1659	Military students	17-24	Serology	17.5%
Torres, 1998 <sup>60</sup>	Mexico	5997	General population	20-90	Serology	81.3%
Us, 1998 <sup>84</sup>	Turkey	364	Out-patients	20-80	Serology	69.0%
Zober, 1998 <sup>113</sup>	Germany	6143	Chemical workers	17-64	Serology	38.2%
Ahmad, 1997 <sup>85</sup>	Bangladesh	181	Out-patients	20-44	Serology	92.0%
Bohmer, 1997 <sup>80</sup>	Netherlands	338	Institutionalized	11-89	Serology	82.8%
		254	Healthy employees	18-50		27.2%
Furuta, 1997 <sup>86</sup>	Japan	1043	Out-patients	16-65	Serology	40.0%
Murray, 1997 <sup>81</sup>	Ireland	4742	General population	12-64	Serology	50.5%
Peach, 1997 <sup>82</sup>	Australia	217	General population	Adult	Serology	30.6%
Rothenbacher, 1997 <sup>87</sup>	Germany	501	Out-patients	15-79	UBT	23.4%
Shinichi, 1997 <sup>84</sup>	Japan	566	Workers	50-55	Serology	79.3%
Taylor, 1997 <sup>42</sup>	US	204	Army personnel	19-37	Serology	37.0%
Andersen, 1996 <sup>35</sup>	Denmark	3589	General population	30-60	Serology	25.9%

Author, Year, Ref No.	Country	No. in study	Population	Age range	Diagnostic Test	Rate
Breuer, 1996 <sup>33</sup>	Germany	260	Blood donors	18-61	Serology	39.2%
Fraser, 1996 <sup>34</sup>	New Zealand	579	Workers	40-64	Serology	56.0%
		190	European			36.0%
		195	Maori			57.0%
		194	Pacific Islanders			73.0%
Malaty, 1996 <sup>34</sup>	Korea	161	Healthy volunteers	20-75	Serology	75.0%
Malaty, 1996 <sup>34</sup>	Russia	213	Out-patients	20-75	Serology	88.0%
Martin-de-Argila, 1996 <sup>35</sup>	Spain	381	Out-patients	5-77	Serology	53.0%
Matysiak-Budnik, 1996 <sup>36</sup>	Poland	656	Blood donors	0-85	Serology	73.0%
Zhang, 1996 <sup>37</sup>	Rural China	2646	General population	35-64	Serology	72.0%
Blecker, 1995 <sup>38</sup>	Belgium	618	Pregnant women out-patients	18-40	Serology	22.6%
	Caucasian	562				62.5%
	Mediterranean	56				85.6%
Chang-Claude, 1995 <sup>38</sup>	China	194	Asymptomatic subjects	15-26	Biopsy	59.5%
Chow, 1995 <sup>39</sup>	Australia	328	General population	25-64	Serology	
			Chinese immigrants			
Gasbarrini, 1995 <sup>44</sup>	San Marino	2237	General population	18-70+	Serology	51.0%
Gilboa, 1995 <sup>45</sup>	Rural Israel	377	General population	30-90	Serology	72.0%
Harris, 1995 <sup>41</sup>	UK	424	Institutionalized	18-106	Serology	87.0%
		267	Healthy controls	18-80+		40.9%
Hyams, 1995[61]	US	1000	Navy and Marine Corps personnel	17-50	Serology	25.0%
	White	730				17.5%
	Black	168				46.4%
	Hispanic	76				44.7%
	Other	24				29.2%
Lambert, 1995 <sup>42</sup>	Australia	122	Institutionalized	19-47	Serology	75.0%
		273	Population controls			23.0%
Murray, 1995 <sup>46</sup>	Ireland	2115	General Practitioner lists	25-64	Serology	57.6%
Replogle, 1995 <sup>48</sup>	California	556	Out-patients	20-39	Serology	27.2%

Author, Year, Ref No.	Country	No. in study	Population	Age range	Diagnostic Test	Rate
Malaty, 1994 <sup>77</sup>	Texas Hispanics Blacks	90 60	Healthy volunteers	19-49	Serology	47.0% 65.0%
Smoak, 1994 <sup>84</sup>	US White Black Hispanic	938 536 324 47	Army recruits	17-26	Serology	26.3% 14.0% 44.0% 38.0%
Teh, 1994 <sup>67</sup>	Taiwan	823	General population	1-40+	Serology	54.4%
Webb, 1994 <sup>78</sup>	UK	471	Male volunteers	18-64	Serology	37.0%
EUROGAST, 1993 <sup>88</sup>	Japan Poland Denmark Minnesota	386 171 157 198	General population	25-34 55-64 25-34 55-64 25-64 55-64 25-64 55-64	Serology	61.0% 89.0% 69.0% 89.0% 15.0% 30.0% 15.0% 34.0%
Malaty, 1992 <sup>79</sup>	Texas Hispanics Blacks Whites	89 89 89	Healthy volunteers	20-75	Serology	65.0% 66.0% 26.0%
Mendall, 1992 <sup>100</sup>	UK	215	In- and out-patients	18-82	Serology	33.0%
Mitchell, 1992 <sup>89</sup>	China	1727	General population	1-50	Serology	44.2%
Graham, 1991 <sup>80</sup>	Texas Blacks Whites	246 239	Healthy volunteers	15-80	Serology	70.0% 34.0%
Polish, 1991 <sup>101</sup>	Colorado	370	Out-patients	15-70	Serology	23.0%
Sitas, 1991 <sup>70</sup>	Wales	749	General population	30-75	Serology	56.9%
Loffeld, 1990 <sup>81</sup>	Netherlands	401	Blood donors	19-65	Serology	35.0%



**Table II-2. Studies assessing the relationship between *Helicobacter pylori* infection and smoking**

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Kikuchi, 1998 <sup>87</sup>	Japan	4361	Public service workers aged 19-65	Ex-smoker, OR=1.0 (0.8-1.2) Current smoker, OR=0.8 (0.7-0.9)	<b>Strength:</b> Control for confounding by logistic regression
Lin, 1998 <sup>87</sup>	Australia	273	General population	Ex-smoker, OR=1.8 (0.9-3.3) Current smoker, OR=1.9 (1.2-2.8)	<b>Strength:</b> Population-based sample; control for confounding by logistic regression <b>Weakness:</b> No association with intensity or age started smoking
Strachan, 1998 <sup>48</sup>	South Wales	1796	Prospective Heart Disease Study volunteers aged 45-59	HP prevalence: never smoke (68.8%), ex-smoker (70.4%), cigar/pipe (68.9%), 1-14 cigs/day (74.4%), 15-24 cigs/day (71.7%), ≥25 cigs/day (69.2%) [p for heterogeneity=0.70]	<b>Weakness:</b> No control for confounding; statistical test used not specified
Zober, 1998 <sup>112</sup>	Germany	6143	Chemical production workers aged 17-64	HP prevalence: never smoke (33.7%), ex-smoker (42.4%), 1-15 cigs/day (37.4%), >15 cigs/day (42.6%)	<b>Weakness:</b> Sample not representative of general population; no control for confounding; statistical tests not utilized
Brenner, 1997 <sup>115</sup>	Germany	501	Out-patients aged 15-79	Former smoker, OR=1.5 (0.8-2.7) Current smoker, OR=1.6 (0.8-3.0)	<b>Strength:</b> control for confounding by logistic regression <b>Weakness:</b> Sample not representative of general population Note – UBT used
Hamajima, 1997 <sup>115</sup>	Japan	192	Out-patients aged 20-70+	Male ex-smoker, OR=2.0 (0.6-7.0) Male current smoker, OR=7.8 (2.0-30.4) Female ex-smoker, OR=0.1 (0.0-2.1) Female current smoker, OR=1.2 (0.2-6.2)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Subjects not representative of general population; no clear biologic mechanism; <10% of females smoked; inconsistent findings by gender

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Murray, 1997 <sup>61</sup>	Ireland	4742	General population sample aged 12-64	Ex-smoker, OR=1.2 (1.0-1.5) Current smoker<20/day, OR=1.0 (0.8-1.2) Current smoker≥20/day, OR=1.3 (1.1-1.7)	<b>Strength:</b> Sample representative of general population; control for confounding by logistic regression; <b>Weakness:</b> Possible bias from low response rate (58%)
Peach, 1997 <sup>62</sup>	Australia	217	General population sample from electoral roll	No association with tobacco use	<b>Strength:</b> Sample representative of general population; control for confounding by logistic regression <b>Weakness:</b> Specific ORs not presented
Rudi, 1997 <sup>116</sup>	Germany	457	Hospital staff aged 16-73	No significant association with tobacco use	<b>Weakness:</b> Sample not representative of general population; specific results not presented
Shinchi, 1997 <sup>54</sup>	Japan	566	Male self-defense officials aged 50-55	HP prevalence: never smoke (81.5%), ex-smoker (75.7%), <25 cigs/day (81.2%), ≥25 cigs/day (77.5%) [p for trend=0.48] (excluding ex-smokers)	<b>Weakness:</b> Sample not representative of general population; low serology specificity (76%); no control for confounding
Fraser, 1996 <sup>81</sup>	New Zealand	579	Workforce survey of subjects aged 40-64	Ex-smoker, RR=1.1 (0.9-1.3) Current smoker, RR=0.9 (0.8-1.1)	<b>Strength:</b> Presented RR estimates adjusted for age and ethnicity <b>Weakness:</b> Not representative of general population; no control for SES factors
Martin-de-Argila, 1996 <sup>75</sup>	Spain	381	Healthy volunteers aged 5-77	Of those who smoked ≥5 cigarettes/day, 54%=HP+ and 46%=HP- (p=0.69)	<b>Weakness:</b> Sample not representative of general population; no control for confounding
Zhang, 1996 <sup>13</sup>	China	2646	General population of rural Chinese aged 35-64	No significant association with smoking	<b>Strength:</b> Subjects representative of general population; control for confounding by logistic regression <b>Weakness:</b> Specific ORs not presented
Chow, 1995 <sup>63</sup>	Australia	328	General population of Chinese immigrants aged >25	Ex-smoker, OR=1.7 Current smoker, OR=1.3 [p>0.05]	<b>Strength:</b> Subjects representative of general population <b>Weakness:</b> Adjusted ORs from logistic regression not presented

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Fontham, 1995 <sup>109</sup>	New Orleans	321	Endoscopy clinic patients aged 18-75	Current smoker, OR=1.7 (1.0-2.9) White smoker, OR=0.6 (0.2-1.8) Black smoker, OR=3.1 (1.5-6.5)	<b>Strength:</b> control for confounding by logistic regression; population of uniform social class <b>Weakness:</b> Sample not representative of general population; inconsistent findings by race Note – biopsy and slide staining used
Gasbarrini, 1995 <sup>64</sup>	San Marino	2237	General population sample aged 20- 70+	No significant association with smoking	<b>Strength:</b> Subjects representative of general population <b>Weakness:</b> ORs not presented; no control for confounding
Gilboa, 1995 <sup>85</sup>	Rural Israel	377	General population	No significant association with smoking	<b>Strength:</b> Subjects representative of general population <b>Weakness:</b> ORs not presented; no control for confounding
Lambert, 1995 <sup>92</sup>	Australia	122	Institutionalized medically and physically handicapped young adults	No significant association with smoking	<b>Strength:</b> Controls representative of general population; ORs adjusted for confounding by logistic regression <b>Weakness:</b> Specific ORs for tobacco not presented
EUROGAST, 1993 <sup>68</sup>	17 Populations	3194	General population Samples aged 25- 34 and 55-64	Ex-smoker, OR=1.2 (0.9-1.5) Current smoker, OR=1.0 (0.8-1.2)	<b>Strength:</b> Subjects representative of general population; control for confounding by logistic regression
Bateson, 1993 <sup>114</sup>	Australia	464	Out-patients with normal upper digestive tracts	HP prevalence: never smoke & ex- smoker (35.5%), current smoker (49.6%) [p<0.01]	<b>Weakness:</b> Sample not representative of general population; no control for confounding Note – biopsy with CLO test used

**Table II-3. Studies assessing the relationship between *Helicobacter pylori* infection and alcohol use**

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Brenner, 1999 <sup>116</sup>	Germany	1785	Participants in German National Health and Nutrition Survey aged 18-88	>0-10 g ethanol/day, OR=0.9 (0.8-1.1) 10-<20 g ethanol/day, OR=0.8 (0.6-1.0) ≥20 g ethanol/day, OR=0.7 (0.6-0.9) Association stronger for wine than beer	<b>Strength:</b> Population-based sample; control for confounding by Cox regression <b>Weakness:</b> Population included only light and moderate drinkers
Brenner, 1999 <sup>117</sup>	Germany	425	Health insurance company and their household members aged 15-69	≤75 g ethanol/wk, OR=0.6 (0.3-1.2) >75 g ethanol/wk, OR=0.3 (0.1-0.8) [p for trend=0.017] Association stronger for wine than beer	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Sample not representative of general population; included members from the same household Note – UBT used
Kikuchi, 1998 <sup>87</sup>	Japan	4361	Public service workers	Occasional drinker, OR=0.9 (0.7-1.1) Ex-drinker, OR=0.7 (0.3-1.6) Current drinker, OR=0.8 (0.7-1.1)	<b>Strength:</b> 87% participation rate <b>Weakness:</b> ORs only adjusted for age and sex
Lin, 1998 <sup>87</sup>	Australia	273	General population	Alcohol consumption, OR=0.7 (0.5-1.1)	<b>Strength:</b> Population-based sample; control for confounding by logistic regression <b>Weakness:</b> Adjusted risks not presented for categorical data
Brenner, 1997 <sup>115</sup>	Germany	501	Out-patients aged 15-79	≤75 g ethanol/wk, OR=0.9 (0.5-1.6) >75 g ethanol/wk, OR=0.3 (0.2-0.7)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Sample not representative of general population Note – UBT used
Murray, 1997 <sup>61</sup>	Ireland	4742	General population sample aged 12-64	< Recommended limit (RL), OR=0.9 (0.7-1.1) ≤2 times RL, OR=1.0 (0.8-1.3) >2 times RL, OR=1.2 (0.9-1.8)	<b>Strength:</b> Sample representative of general population; control for confounding by logistic regression; <b>Weakness:</b> Possible bias from low response rate (58%)

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Peach, 1997 <sup>62</sup>	Australia	217	General population sample from electoral roll	No association with alcohol use	<b>Strength:</b> Sample representative of general population; control for confounding by logistic regression <b>Weakness:</b> Specific ORs not presented
Shinichi, 1997 <sup>64</sup>	Japan	566	Male self-defense officials aged 50-55	HP prevalence: never drink (80.0%), ex-drinker (61.9%), <50 ml/day (81.5%), ≥50 ml/day (78.0%) [p for trend=0.54] (excluding ex-drinkers)	<b>Weakness:</b> Sample not representative of general population; low serology specificity (76%); no control for confounding
Fraser, 1996 <sup>65</sup>	New Zealand	579	Workforce survey of subjects aged 40-64	Drinkers, RR=0.9 (0.8-1.1)	<b>Strength:</b> Presented RR estimates adjusted for age and ethnicity <b>Weakness:</b> Not representative of general population; no control for SES factors
Martin-de-Argila, 1996 <sup>65</sup>	Spain	381	Healthy volunteers aged 5-77	Of those who drank >60 g ethanol/day, 55%=HP+ and 45%=HP- [p=0.78]	<b>Weakness:</b> Sample not representative of general population; no control for confounding
Chow, 1995 <sup>63</sup>	Australia	328	General population of Chinese immigrants aged ≥25	Drink < weekly, OR=0.8 Drink weekly, OR=0.9 [p>0.05]	<b>Strength:</b> Subjects representative of general population <b>Weakness:</b> Adjusted ORs from logistic regression not presented
Fontham, 1995 <sup>109</sup>	New Orleans	321	Endoscopy clinic patients aged 18-75	1-2 drinks/wk, OR=0.4 (0.2-0.8) ≥3 drinks/wk, OR=0.6 (0.3-1.4) [p for trend=0.25]	<b>Strength:</b> control for confounding by logistic regression; population of uniform social class <b>Weakness:</b> Sample not representative of general population Note – biopsy and slide staining used
Lambert, 1995 <sup>92</sup>	Australia	122	Institutionalized medically and physically handicapped young adults	No significant association with alcohol use	<b>Strength:</b> Controls representative of general population; ORs adjusted for confounding by logistic regression <b>Weakness:</b> Specific ORs for alcohol not presented

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
EUROGAST, 1993 <sup>68</sup>	17 Populations	3194	General population sample aged 25-34 and 55-64	Some alcohol, OR=1.0 (0.8-1.2)	<b>Strength:</b> Subjects representative of general population; control for confounding by logistic regression

**Table II-4. Studies assessing the relationship between *Helicobacter pylori* infection and diet**

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Jarosz, 1999 <sup>123</sup>	Poland	51	<i>H. pylori</i> infected patients with chronic gastritis aged 21-60	8/27 (30%) had apparently successful <i>H. pylori</i> eradication after 4 weeks of vitamin C treatment (5 g/day) compared with 0/24 untreated controls [p=0.01]	<b>Strength:</b> Patients randomized to treatment; levels of vitamin C measured in gastric juice and serum <b>Weakness:</b> Follow-up limited to 4 weeks post treatment
Begue, 1998 <sup>127</sup>	Peru	104	Gastroenterology clinic patients aged 0-17	<b>Food from street vendors:</b> never [referent]; once/month, OR=2.7 (1.0-7.6); once/week, OR=2.5 (0.2-99)	<b>Strength:</b> ORs adjusted for age by stratification <b>Weakness:</b> Subjects not representative of general population, no control for other confounding factors Note – biopsy and stain used
Malaty, 1998 <sup>124</sup>	Sweden	270 twin pairs	Swedish Twin Registry adults, mean age=65.5	Consumption of high levels of ascorbic acid associated with <i>H. pylori</i> infection in twin reared apart. (p=0.04)	<b>Strength:</b> Study of twin pairs controlled for genetic effects <b>Weakness:</b> used paired t test – no adjustment for confounding
Goodman, 1997 <sup>121</sup>	Columbia	684	Population-based sample of rural children aged 2-9 years	<b>Servings of fruits &amp; vegetables/day:</b> ½-1 ½, OR=19.1 (4.0-91.9); 2-2 ½, OR=1.8 (1.0-3.4); 3-5 ½, OR=1.0 [referent]; 6-12, OR=0.6 (0.3-1.4) <b>Vitamin C in mg/day:</b> 10-39, OR=7.2 (1.5-34.1); 40-79, OR=1.3 (0.7-2.4); 80-119, OR=1.0 [referent]; 120-641, OR=0.6 (0.3-1.1) <b>Beta-carotene in IU/day:</b> 96-299, OR=3.1 (1.2-7.9); 300-599, OR=2.3 (1.1-5.1); 600-899, OR=1.9 (0.9-3.8); ≥900, 1.0 [referent]	<b>Strength:</b> Population-based sample; control for confounding by logistic regression <b>Weakness:</b> Possibility for differential misclassification if mothers of HP-children more socially aware of proper dietary responses; diet difficult to classify; variables highly correlated Note – UBT used

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Hamajima, 1997 <sup>113</sup>	Japan	192	Out-patients aged 20-70+	Males: rice for breakfast, OR=3.7 (1.3-10.8); soybean paste soup every day, OR=5.2 (1.8-15.2) Females: pickled Chinese cabbage weekly, OR=2.8 (1.1-7.5); lettuce, OR=2.9 (1.1-7.8)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Subjects not representative of general population; no clear biologic mechanism
Peach, 1997 <sup>62</sup>	Australia	217	General population sample from electoral roll	No association with vegetarian diet	<b>Strength:</b> Sample representative of general population; control for confounding by logistic regression <b>Weakness:</b> Specific ORs not presented
Shinchi, 1997 <sup>54</sup>	Japan	566	Male self-defense officials aged 50-55	HP prevalence for Tofu: low (88.6%), middle (76.7%), high (76.1%) [p for trend=0.01, but no longer significant after Bonferroni correction] No other food items related to HP+	<b>Strength:</b> Adjusted for rank (SES measure) by the direct method <b>Weakness:</b> Sample not representative of general population; low serology specificity (76%); multiple comparisons
Goodman, 1996 <sup>122</sup>	Columbia	684	Population-based sample of rural children aged 2-9 years	Raw vegetables in servings/day: 2, OR=1.5 (0.8-2.9); ≥3, OR=2.0 (0.9-4.6) Fruits & vegetables in servings/day: ≥2, OR=0.1 (0.0-0.3) Milk : ≥1/2 cups/day, OR=0.5 (0.3-1.1)	<b>Strength:</b> Population-based sample; control for confounding by logistic regression <b>Weakness:</b> Possibility for differential misclassification if mothers of HP- children more socially aware of proper dietary responses; diet difficult to classify; variables highly correlated Note – UBT used
Zhang, 1996 <sup>11</sup>	China	2646	General population aged 35-64	HP prevalence for eat sour pancakes: yes (76%), no (70%) [p<0.05]	<b>Strength:</b> Subjects representative of general population; control for confounding by logistic regression



Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Fonham, 1995 <sup>109</sup>	New Orleans	321	Endoscopy clinic patients aged 18-75	<b>Fruits/wk:</b> 7-14, OR=0.8 (0.4-1.6); $\geq 14$ , OR=0.5 (0.2-1.0) [p for trend=0.04] <b>Vitamin C</b> in mg/day: Middle 2 quartiles, OR=0.8 (0.4-1.5); Highest quartile, OR=0.4 (0.2-0.8) [p for trend=0.02]	<b>Strength:</b> Control for confounding by logistic regression; population of uniform social class; used validated reduced dietary questionnaire <b>Weakness:</b> Sample not representative of general population <b>Note</b> – biopsy and slide staining used
Hopkins, 1993 <sup>125</sup>	Chile	1815	General population <35 years of age	<b>Uncooked vegetables</b> , OR=3.2 (1.9-5.7) <b>Uncooked shellfish</b> , OR=1.3 (1.1-1.7)	<b>Strength:</b> Subjects representative of general population; control for confounding by logistic regression
Webberley, 1992 <sup>246</sup>	UK	241	Out-patients aged 18-70	HP prevalence similar for Asian vegans (36%) and Asian meat eaters (32%) HP prevalence higher in Asians than Caucasians (18%)	<b>Weakness:</b> Subjects not representative of general population; no control for confounding; statistical methods not described

**Table II-5. Studies assessing the relationship between *Helicobacter pylori* infection and occupational exposures**

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Monés, 1999 <sup>40</sup>	Spain	180 44 189	Gastroenterologists Non-gastroenterologists Healthy controls	HP prevalence: gastroenterologists (53.3%) [endoscopists (53.3%); non-endoscopists (53.5%)], non-gastroenterologists (50.0%), controls (51.9%)	<b>Strength:</b> Comparison of endoscopists with non-endoscopists and gastroenterologists with other physicians as well as controls; <b>Weakness:</b> No control for confounding Note – UBT used
Lin, 1998 <sup>30</sup>	Australia	92 40 295 39 107	Dentists Dental nurses Controls Gastroenterologists Endoscopy nurses	Dentists vs controls, OR=0.6 (0.3-1.1) Dental nurses vs controls, OR=1.0 (0.4-2.9) HP prevalence: gastroenterologists (80%) vs dentists (21%) [p<0.01], especially those employed ≥11 years HP prevalence for endoscopy (38%) vs dental (23%) nurses [p>0.05]	<b>Strength:</b> Representative sample of dentists and dental nurses; population-based sample of controls; control for confounding by age and sex by logistic regression <b>Weakness:</b> Assumes exposure differences due to occupational rather than some other exposure
Nishikawa, 1998 <sup>42</sup>	Japan	92 29 101	Gastroenterologists Endoscopy nurses Healthy controls	HP prevalence: endoscopy personnel (29.8%), controls (24.8%) [p=0.406]	<b>Strength:</b> Controls matched to endoscopy personnel by age <b>Weakness:</b> No control for confounding factors other than age
Shelley, 1998 <sup>38</sup>	US	54	Anesthesiologists	HP prevalence 4% in anesthesiologists compared to 19% in 2 published US control groups [p<0.01]	<b>Weakness:</b> no control for confounding; controls groups from different population than anesthesiologists
Bohmer, 1997 <sup>38</sup>	Netherlands	254	Employees of institutes for Intellectually Disabled aged 18-50	HP prevalence: staff with close physical contact to patients (31.6%) vs other staff (14.1%) [p=0.002] OR=2.8 (1.1-7.0) for those employed >5 years	<b>Weakness:</b> Statistical tests used not specified, no apparent control for confounding

Author, Year, Ref No,	Country	No. in Study	Population	Outcome	Comments
Braden, 1997 <sup>141</sup>	Germany	922 538 169 66 413	Gastroenterologist Other physicians Endoscopy nurses Other nurses Controls	Case/control comparisons: endoscopy physicians vs controls, OR=1.6 (1.3-2.1); other physicians vs controls, OR=1.5 (1.2-2.0); endoscopy nurses vs controls, OR=1.8 (1.2-2.6); other nurses vs controls, OR=1.6 (1.0-2.6); endoscopy staff vs general medical staff, OR=1.1 (0.9-1.3)	<b>Strength:</b> Comparison of endoscopists with other physicians as well as controls; control for confounding by age by logistic regression <b>Weakness:</b> Study can't differentiate risk between transmission by endoscopy and colonoscopy since these physicians do both in Germany Note – UBT used
Potts, 1997 <sup>135</sup>	UK	30 30	Gastroenterologists Respiratory doctors	15/30 gastroenterologists & 3/30 respiratory physicians had positive breath tests for HP [p<0.001] Risk may be lower for gastroenterologists who wear gloves	<b>Weakness:</b> Specifics of population selection not clear; statistical tests used not specified
Rudi, 1997 <sup>116</sup>	Germany	110 272 75	1) Nonmedical staff 2) Medical staff 3) Endoscopy staff	HP prevalence: Group 1 (35.5%), Group 2 (34.6%), Group 3 (24.0%). No significant differences in the 3 groups	<b>Strength:</b> Adjusted for age, duration of experience, and number of years worked in unit <b>Weakness:</b> Statistical tests used not specified
Friis, 1996 <sup>138</sup>	Sweden	151 138	Sewage workers Other municipal workers	No increased risk for HP infection among sewage workers, RR=1.0 (0.7-1.5) and OR=0.90 (CI=0.5-1.5)	<b>Strength:</b> RRs calculated, ORs controlled for confounding by age and region by logistic regression; referent group of workers frequency matched by age, SES, and region <b>Weakness:</b> No control for confounding effects of other potential risk factors
Goh, 1996 <sup>134</sup>	Malaysia	82 53	Endoscopy staff Non-endoscopy staff	Endoscopy staff had a higher prevalence of HP than non-endoscopy staff (32.9% vs 11.3%, p=0.004)	<b>Weakness:</b> No control for confounding factors; mean age 2.9 years older for endoscopy staff Note – UBT used

Author, Year, Ref No,	Country	No. in Study	Population	Outcome	Comments
Liu, 1996 <sup>135</sup>	China	1050 702	Medical staff Healthy out-patient controls	Medical staff vs controls, OR=2.9 (2.4-3.4); endoscopists vs internists, OR=2.2 (1.4-3.7); endoscopist vs general nurses, OR=2.4 (1.4-4.1) Worked as an endoscopist for $\geq 5$ years, OR=3.7 (1.4-10.1)	<b>Strength:</b> Comparison of endoscopists with other medical staff and "healthy" controls; includes a large variety of medical staff <b>Weakness:</b> No control for confounding other than age
Su, 1996 <sup>136</sup>	Taiwan	70 64	Endoscopists Other physicians	HP prevalence: endoscopists (80.0%) vs other physicians (51.6%) [ $p<0.05$ ] HP prevalence: $< 30$ endoscopies/week (70.3%) vs $\geq 30$ endoscopies/week (90.9%) [ $p=0.01$ ]	<b>Strength:</b> Excluded subjects with serology values in the "gray zone"; control doctors has similar exposures except for endoscopy <b>Weakness:</b> No comparison with general population controls
Banatvala, 1995 <sup>137</sup>	Wales	70 47 62 179	Dentists Clinical students Pre-clinical students Matched controls	HP prevalence: dentists (16%), clinical dental students (6%), pre-clinical dental students (10%). Case/control comparisons: Dentists (OR=0.6, CI=0.2-1.5), clinical students (OR=1.0, CI=0.3-3.7), pre-clinical students (OR=1.0, CI=0.2-5.4)	<b>Strength:</b> Controls matched on age, sex, SES; matched analysis controlled for these confounding factors <b>Weakness:</b> Controls not representative of general population; response rate in dentists=69%
Chong, 1994 <sup>138</sup>	US	111 11 510	Gastroenterologists Endoscopy nurses Blood donors	HP prevalence: gastroenterologists/endoscopy nurses (53%) vs controls (14%) [ $p<0.001$ ] HP prevalence: gastroenterologists (52%), endoscopy nurses (55%)	<b>Strength:</b> Subgroup analyses were done on "comparable" endoscopy professionals and controls <b>Weakness:</b> Volunteer control group obtained from one geographic area (Charlottesville, VA) may not be comparable to endoscopy group attending advanced course in Miami, FL - lacked controls except for US born Caucasians

Author, Year, Ref No,	Country	No. in Study	Population	Outcome	Comments
Lin, 1994 <sup>138</sup>	Australia	39 107 25 42 273	Gastroenterologists Endoscopy nurses Internists General nurses Population controls	Case/control comparisons: gastroenterologists, OR=5.0 (CI=2-12); Internists, OR=1.0 (0.3-3.1); endoscopy nurses, OR=0.6 (0.3-1.2); general nurses, OR=0.9 (0.3-2.5) Gastroenterologists vs internists, OR=1.8 (1.1-4.6)	<b>Strength:</b> Controls representative of general population; subjects age- and sex matched Caucasians; logistic regression analysis controlled for these confounding factors
Malaty, 1992 <sup>139</sup>	US	239	Dental workers volunteers from Texas	Dentists + dental hygienist vs. assistants + dental students, OR=2.3 (1.0-5.3) HP prevalence: white dental workers (16%), nonwhite dental workers (46%); white community (27%), black community (58%)	<b>Strength:</b> Compared dentists with other dental workers as well as with asymptotic controls; control for confounding by logistic regression <b>Weakness:</b> Control group may not be comparable on age and other factors
Mitchell, 1989 <sup>139</sup>	Australia	33 68 35 715	Gastroenterologists Endoscopy nurses General practitioners Normal blood donors	HP prevalence: gastroenterologists (51%) vs. blood donors (21%) [ $p<0.01$ ]; endoscopy nurses (19%) and general practitioners (28%) not different from blood donors	<b>Strength:</b> Comparison of endoscopists with endoscopy nurses, and general practitioners with volunteer controls <b>Weakness:</b> Control group not representative of general population, may be unusual since highest HP+ found in the youngest age group (21-30)

**Table II-6. Studies assessing the relationship between *Helicobacter pylori* infection and waterborne exposures**

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Elitsur, 1998 <sup>145</sup>	US	1164	West Virginia children	Source of water supply, city or well, was not significantly related to HP status	<b>Strength:</b> large study of children; controlled for confounding by multiple regression <b>Weakness:</b> Subjects not representative of "healthy" children; bias may have occurred in selection of participants; results hard to interpret
Goodman, 1996 <sup>122</sup>	Columbia	684	Population-based sample of rural children aged 2-9 years	<b>Lifetime drinking water source:</b> Well/pump only [referent] Tap, OR=1.0 (0.5-2.0) Stream, OR=2.8 (1.2-6.8) <b>Swims in rivers/streams:</b> < once a year [referent] several times /year, OR=3.3 (1.2-9.4) <b>Swims in swimming pools:</b> < once a year [referent] several times /year, OR=3.6 (1.5-8.5)	<b>Strength:</b> Population-based sample; control for confounding by logistic regression <b>Weakness:</b> Possibility for differential misclassification if mothers of HP- children more socially aware of proper hygiene responses; variables highly correlated Note – UBT used
Malaty, 1996 <sup>74</sup>	Korea	161	Adult volunteers aged 20-75	<b>Water source:</b> well [referent] City, OR=1.4 (1.2-2.6) Bottled, OR=1.7 (1.4-6.8)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Sample not representative of general population; over representation of middle class
Matysiak-Budnik, 1996 <sup>76</sup>	Poland	181	Healthy volunteers aged 0-34	Used well water, OR=1.1 (0.2-7.3)	<b>Weakness:</b> Sample not representative of general population; no control for confounding; high rate of HP+
Zhang, 1996 <sup>13</sup>	China	2646	General population of rural adults aged 35-64	HP prevalence - drinking water source: Ponds or ditches (88%) Deep wells (73%) Surface wells (72%) No statistically significant differences	<b>Strength:</b> Subjects representative of general population; control for confounding by logistic regression <b>Weakness:</b> Only a small percentage obtained their water from ditches

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Teh, 1994 <sup>67</sup>	Taiwan	555 268	Adults Children General population	Drinking water source: Tap water [referent] River water, OR=0.9 (0.6-1.5) Well water, OR=1.2 (0.8-1.7)	<b>Strength:</b> Subjects representative of general population; age-adjusted ORs <b>Weakness:</b> No control for other confounding factors
Hopkins, 1993 <sup>125</sup>	Chile	1815	General population <35 years of age	Swimming near contaminated beaches, OR=1.1 (0.8-1.5) Bathing in fresh water rivers, irrigation ditches, or lakes, OR=1.4 (0.8-2.4)	<b>Strength:</b> Subjects representative of general population; control for confounding by logistic regression
Klein, 1991 <sup>124</sup>	Peru	407	Children aged $\leq 12$ of low and high SES	External vs. internal water sources, OR=3.4 [p=0.001] Municipal vs. community wells (high income only), OR=12.6 [p=0.02]	<b>Strength:</b> Control for age by logistic regression <b>Weakness:</b> Subjects not representative of general population; confounded by SES as no subject of high SES had external water sources Note – UBT used

**Table II-7. Studies assessing the relationship between *Helicobacter pylori* infection and exposure to pets and other animals**

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Dore, 1999 <sup>18</sup>	Sardinia	123 30 509	Shepherds Family members Blood donors aged 17-75	HP prevalence among shepherds (98%) greater than among family members (73%), OR=21.9 (4.5-106) or blood donors (43%), OR=78.8 (20-311)	<b>Strength:</b> Serology confirmed by endoscopy <b>Weakness:</b> Controls not representative of general population, no control for confounding
McIsaac, 1999 <sup>18</sup>	Canada	15779	National population health survey	No association between dog/cat ownership and history of peptic ulcer disease (OR=1.1, CI=0.9-1.4)	<b>Strength:</b> Sample representative of general population; large study population; control for confounding by logistic regression <b>Weakness:</b> Dogs and cats grouped together; only asked about current pet ownership; diagnosis of peptic ulcer not independently validated
Begue, 1998 <sup>17</sup>	Peru	104	Gastroenterology patients aged 0-17	No association with exposure to domestic animals (dogs, cats, birds)	<b>Weakness:</b> Subjects not representative of general population, no control for confounding factors Note – biopsy and stain used
Bode, 1998 <sup>18</sup>	Germany	685	General population sample of preschool children	<b>Has pets</b> (OR=1.1, CI=0.6-2.4) <b>Has cat</b> (OR=1.9, CI=0.7-5.1) <b>Has rabbit</b> (OR=1.7, CI=0.6-4.7)	<b>Strength:</b> Population-based sample; control for confounding by logistic regression <b>Weakness:</b> Prevalence of infection only 6.3%; little power to detect significant association Note – UBT used
Luzza, 1998 <sup>91</sup>	Rural Italy	705	Adult and Children Out-patients aged 1-87	No difference in the percentage of HP+ and HP- subjects who had household pets during childhood	<b>Weakness:</b> Subjects not representative of general population; no control for confounding; no statistical tests



Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Rothenbacher, 1998 <sup>85</sup>	Germany	337	Adult students aged 50-80	No association between HP infection and occupational handling of animals or having a pet or a dog in the household during childhood HP prevalence - cat in the house during childhood: No (30.7%) Yes (44.7%) [p=0.017]	<b>Strength:</b> Assess current HP status with UBT <b>Weakness:</b> Not representative of general population; no control for confounding; no detail of statistical test used
Peach, 1997 <sup>63</sup>	Australia	217	General population sample from electoral roll	No association with occupational or recreational contact with animals	<b>Strength:</b> Sample representative of general population; control for confounding by logistic regression <b>Weakness:</b> Specific ORs not presented
Rothenbacher, 1997 <sup>97</sup>	Germany	501	Out-patients aged 15-79	No association between HP infection and having a pet, dog, or cat in the household (compared % positivity)	<b>Weakness:</b> Sample not representative of general population; no control for confounding except by age Note – UBT used
Goodman, 1996 <sup>122</sup>	Columbia	684	Population-based sample of rural children aged 2-9 years	<b>Household has rabbits</b> (OR=0.3, CI=0.1-0.7) <b>Child plays with sheep</b> (OR=4.5, CI=0.7-30.5)	<b>Strength:</b> Population-based sample; control for confounding by logistic regression <b>Weakness:</b> Estimate for contact with sheep lacks precision Note – UBT used
Staat, 1996 <sup>127</sup>	US	2581	6-19 years old participants in National survey	HP prevalence – any pets in household: Any (19.0%) None (31.5%) [p<0.05]	<b>Strength:</b> Population-based sample; prevalences weighted to account for oversampling and lack of response
Webb, 1996 <sup>200</sup>	UK	447	Male volunteers aged 18-65	Pets during childhood: None [referent] Cat (OR=1.4, CI=0.7-2.9) Other (OR=0.6, CI=0.6-2.5)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Subjects not representative of general population
Webb, 1994 <sup>18</sup>	UK	471	Male volunteers aged 18-65	HP prevalence - household pets: No (34.7%) Yes (38.2%) [p=0.5]	<b>Weakness:</b> Subjects not representative of general population; no control for confounding

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Graham, 1991 <sup>40</sup>	Texas Blacks Whites	246 239	Healthy volunteers aged 15-80	Have pets, OR=0.5 [p=0.009]	Strength: control for confounding by logistic regression Weakness: Subjects not representative of general population; owning pets thought to be surrogate for high social class Note -- UBT used

**Table II-8. Studies assessing the relationship between *Helicobacter pylori* infection and hygiene practices**

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Luzza, 1998 <sup>93</sup>	Rural Italy	705	Out-patients	Possession of a bathroom (HP+=85%, HP-=92%), a refrigerator (HP+=43%, HP-= 62%), and a hot water supply (HP+=26%, HP-= 48%) during childhood was reported by fewer HP+ than HP- subjects (not significant after adjustment for age)	<b>Weakness:</b> Subjects not representative of general population; no control for confounding; statistical results not presented
Peach, 1997 <sup>82</sup>	Australia	217	General population sample from electoral roll	Did not usually wash hands after toilet, OR=4.1 (0.5-35.0)  No association with frequency of sharing toothbrush or cup or washing hands before eating	<b>Strength:</b> Sample representative of general population; control for confounding by logistic regression <b>Weakness:</b> only a small number reported infrequent handwashing; ORs not presented for sharing toothbrush or cup or washing hands before eating
Rothenbacher, 1997 <sup>97</sup>	Germany	501	Out-patients aged 15-79	HP prevalence - shared towel with another household member: Yes (15.9%), No (25.9%) [p=0.199]	<b>Weakness:</b> Sample not representative of general population; no control for confounding except by age Note - UBT used
Breuer, 1996 <sup>95</sup>	Germany	260	Blood donors aged 18-61	No WC in house now, OR=1.0 (0.4-3.0) No WC in house age 8, OR=2.6 (1.1-6.4) No hot water now, OR=3.2 (0.2-35.6) No hot water age 8, OR=1.8 (0.9-3.7)	<b>Strength:</b> All subjects approached participated <b>Weakness:</b> Subjects not representative of general population; no control for confounding;
Czkwianianc, 1996 <sup>130</sup>	Poland	240	Children aged 6 months-17 years who were patients at hospitals and clinics	Prevalence of HP+ higher in children who lived in households where the level of hygiene and sanitation were the poorest [p<0.005]	<b>Weakness:</b> Sample not representative of general population; no control for confounding; statistical tests not specified

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Goodman, 1996 <sup>122</sup>	Columbia	684	Population-based sample of rural children aged 2-9 years	Shares cups, OR=1.8 (1.1-3.1) Mother rarely washes hands with soap, OR=2.7 (1.1-6.6) Location of latrine relative to hand washing facility: < 25 meters [referent] > 25 meters, OR=1.6 (0.8-2.9) No latrine, OR=2.2 (0.9-5.3)	<b>Strength:</b> Population-based sample; control for confounding by logistic regression <b>Weakness:</b> Possibility for differential misclassification if mothers of HP-children more socially aware of proper hygiene responses; exposures difficult to classify; variables highly correlated Note – UBT used
Chow, 1995 <sup>61</sup>	Australia	328	General population of Chinese immigrants aged >25	Used chopsticks, OR=2.5 [p<0.001]	<b>Strength:</b> Subjects representative of general population; <b>Weakness:</b> Adjusted ORs from logistic regression not presented
Mcgraud, 1995 <sup>151</sup>	Western Africa	38 97	HP+: mother and child HP-: mother and child	Premastication of infant's food by mother, OR=2.9 (0.9-9.0)	<b>Weakness:</b> Pilot study embedded in review paper; no details for design or analysis provided; no apparent control for confounding factors Note – serology and/or breath test was used
Teh, 1994 <sup>67</sup>	Taiwan	555 268	Adults Children General population	Have other than flushing type toilet, OR=1.0 (0.6-1.6)	<b>Strength:</b> Subjects representative of general population; age-adjusted ORs <b>Weakness:</b> No control for other confounding factors
Webb, 1994 <sup>14</sup>	UK	471	Male volunteers aged 18-65	HP prevalence – bathroom: No (42.0%) vs. Yes (35.1%) [p=0.2] HP prevalence – inside toilet: No (40.3%) vs. Yes (35.5%) [p=0.3]	<b>Weakness:</b> Subjects not representative of general population; no control for confounding

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Hammermeister <sup>132</sup>	Germany	64	Submarine crews	HP prevalence – German submarine crews (31.7%) vs. German air force recruits (16.2%), OR=2.4 [p<0.05]	<b>Strength:</b> Prospective study, with 3-4 blood samples in a 1 year period - no seroconversion in any group <b>Weakness:</b> Authors used logistic regression to control for age, but not SES
	France	74 51 135	New Air Force staff Infantry ≥3 years New Infantry	HP prevalence – French infantry regular officers (13.7%) vs. French infantry recruits (18.5%) NS	
Mendall, 1992 <sup>100</sup>	UK	215	Subjects aged 18-82 attending a health-screening clinic	No fixed hot water supply in house at age 8, OR=4.3 (1.9-10.0)	<b>Strength:</b> Control for confounding by logistic regression; age 8 used as mid-point of childhood and to enhance recall <b>Weakness:</b> Subjects not representative of general population

**Table II-9. Studies assessing the relationship between *Helicobacter pylori* infection and density/crowding**

Author, Year, Ref No.	Country	No. In Study	Population	Outcome	Comments
Alagathanam, 1999 <sup>55</sup>	India	354	General upper class population aged 12-70+	HP prevalence – Family size <5 (45.4%) vs. ≥5 (56.7%) [p<0.05]	<b>Strength:</b> Representative of an urban class population <b>Weakness:</b> No control for confounding; no adjustment for multiple subjects from same household
Kikuchi, 1998 <sup>87</sup>	Japan	4361	Public service workers	Sibship size: 1 [referent] 2-3, OR=1.2 (0.8-1.6) 4+, OR=1.5 (1.0-2.1) [p=0.013]	<b>Strength:</b> 87% participation rate <b>Weakness:</b> ORs only adjusted for age and sex
Luzza, 1998 <sup>91</sup>	Rural Italy	705	Out-patients	Number of people/room during childhood: HP+=3.2±2.4, HP- =2.1±1.9 [p<0.5] Number of siblings: HP+=4.6±2, HP-=3.7±2 [p<0.05]	<b>Weakness:</b> Subjects not representative of general population; control for confounding in logistic regression, but ORs based on continuous variables not that informative compared to means
Malaty, 1998 <sup>124</sup>	Sweden	270 twin pairs	Swedish Twin Registry adults, mean age=65.5	Crowded living conditions and poor economic conditions associated with HP+ in twins reared apart (p=0.02)	<b>Strength:</b> Study of twin pairs controlled for genetic effects <b>Weakness:</b> used paired t test – no adjustment for confounding
Rothenbacher, 1998 <sup>85</sup>	Germany	337	Adults students aged 50-80	Shared a bed with siblings or parents during childhood, OR=2.6 (1.1-6.1)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Not representative of general population Note – UBT used
Stroffolini, 1998 <sup>86</sup>	Italy	1659	Military students	≥1 sibling, OR=1.3 (1.0-1.7)	<b>Strength:</b> control for confounding by logistic regression <b>Weakness:</b> sample not representative of general population; sample may be too heterogeneous

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Torres, 1998 <sup>60</sup>	Mexico	9116	General population aged 1-39	Crowding (persons/room): 1.5 [referent] 1.6-3.5, OR=1.3 (1.1-1.5) ≥3.6, OR=1.4 (1.2-1.6)	<b>Strength:</b> Sample representative of general population; age-adjusted ORs <b>Weakness:</b> no control for other confounding factors
Peach, 1997 <sup>63</sup>	Australia	217	General population sample from electoral roll	≥6 people in household at age 0-16, OR=2.5 (1.1-5.5)	<b>Strength:</b> Sample representative of general population; control for confounding by logistic regression
Rothenbacher, 1997 <sup>67</sup>	Germany	501	Out-patients aged 15-79	Sibship size, 0 [referent] 1, OR=1.2 (0.5-2.7) 2-3, OR=1.5 (0.7-3.4) ≥4, OR=2.7 (1.2-6.1)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Sample not representative of general population Note – UBT used
Shinchi, 1997 <sup>64</sup>	Japan	566	Male self-defense officials aged 50-55	HP prevalence – rank Low (82.5%) Middle (75.2%) High (75.0%) [p for trend=0.48]	<b>Weakness:</b> Sample not representative of general population; low serology specificity (76%); no control for confounding
Breuer, 1996 <sup>65</sup>	Germany	260	Blood donors aged 18-61	A) ≥1 child in household at present, OR=1.8 (1.0-3.2) B) >1 person/room now, OR=2.4 (1.2-4.9) C) >1 person/room at age 8, OR=2.1 (1.1-4.3)	<b>Strength:</b> All subjects approached participated; control for confounding by logistic regression for A and C <b>Weakness:</b> Subjects not representative of general population; only control for age for B
Clemens, 1996 <sup>154</sup>	Bangladesh	257	Population-based sample of children aged 2-5	HP+ children had a higher median number of persons per sleeping room (3.8 vs. 3.2) [p<0.05]	<b>Strength:</b> Sample representative of general population; control for confounding <b>Weakness:</b> Population may have been too homogeneous to see striking SES differences
Czkwianiance, 1996 <sup>150</sup>	Poland	240	Children aged 6 months-17 years who were patients at hospitals and clinics	Prevalence of HP+ higher in children who lived in households where number of persons per room was higher [p<0.005]	<b>Weakness:</b> Sample not representative of general population; no control for confounding; statistical tests not specified

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Goodman, 1996 <sup>122</sup>	Columbia	684	Population-based sample of rural children aged 2-9 years	Number of persons in family: 3 [referent] 4-5, OR=3.7 (1.2-11.4) 6-8, OR=6.3 (1.9-20.5) 9-15, OR=8.0 (2.2-28.9)	<b>Strength:</b> Population-based sample; control for confounding by logistic regression <b>Note</b> – UBT used
Malaty, 1996 <sup>14</sup>	Korea	161	Adult volunteers aged 20-75	≥5 family members in house, OR=1.2 (1.1-4.5)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Sample not representative of general population; over representation of middle class
Malaty, 1996 <sup>14</sup>	Russia	213	Asymptomatic adults aged 20-75	Crowding index, Low [referent] Moderate, OR=0.7 (0.6-2.2) High, OR=1.4 (1.1-4.5)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Subjects not representative of general population; Russian society is very homogeneous
McCallion, 1996 <sup>153</sup>	Ireland	367	3-15 year old outpatients	<b>Household density</b> (persons/room), <0.7 [referent] 0.7-1.0, OR=2.0 (1.0-3.9) >1.0, OR=3.4 (1.7-6.6) <b>Sharing a bed with a parent, Never [referent]</b> 1-2 nights/week, OR=2.3 (1.2-4.3) >2 nights/week, OR=3.0 (1.4-6.4)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Subjects not representative of general population
Staat, 1996 <sup>147</sup>	US	2581	6-19 year old participants in National survey	<b>Crowding index</b> (persons/room) <0.5 [referent] 0.5-0.99, OR=1.8 (1.0-3.4) 1.0-1.99, OR=2.1 (1.3-3.4) ≥2, OR=5.6 (2.9-10.9)	<b>Strength:</b> Population-based sample; control for confounding by logistic regression



Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Replogle, 1995 <sup>45</sup>	California	556	Health plan members aged 20-39	Number of children Lived with as a child, Didn't live with children [referent] 1-2, OR=1.1 (1.0-1.2) 3-4, OR=1.3 (1.1-1.5) ≥5, OR=1.4 (1.2-1.5) [p for trend≤0.01] Lived with children as an adult, OR=1.9 (1.4-2.6)	<b>Strength:</b> Calculated RRs <b>Weakness:</b> Subjects not representative of general population; no control for confounding
Malaty, 1994 <sup>77</sup>	Texas	150	Black & Hispanic Healthy volunteers aged 19-49	Crowding index, Low [referent] Middle, OR=3.1 (2.1-4.1) High, OR=4.5 (3.3-5.7)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Subjects not representative of general population
Teh, 1994 <sup>67</sup>	Taiwan	268	Children General population	Sibship size, 0-1 [referent] 2, OR=1.6 (0.7-3.8) ≥3, OR=3.9 (1.6-9.5)	<b>Strength:</b> Subjects representative of general population; age-adjusted ORs <b>Weakness:</b> No control for other confounding factors
Webb, 1994 <sup>78</sup>	UK	471	Male volunteers aged 18-65	Crowding - >1 per room, OR=1.8 (1.1-4.0) Shared a bed, OR=1.6 (1.0-2.6)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Subjects not representative of general population; collinearity of density measures

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Hammermeister 1992 <sup>132</sup>	Germany	64	Submarine crews	HP prevalence – German submarine crews (31.7%) vs. German air force recruits (16.2%), OR=2.4 [p<0.05]	Strength: Prospective study, with 3-4 blood samples in a 1 year period - no seroconversion in any group Weakness: Authors used logistic regression to control for age, but not SES
	France	74 51 135	New Air Force staff Infantry ≥3 years New Infantry	HP prevalence – French infantry regular officers (13.7%) vs. French infantry recruits (18.5) NS	
Mendall, 1992 <sup>100</sup>	UK	215	Subjects aged 18-82 attending a health-screening clinic	Persons per room in childhood <0.7 [referent] 0.7-0.99, OR=1.4 (0.4-4.4) 1.0-1.29, OR=4.0 (1.4-11.8) ≥1.3, OR=6.2 (1.8-18.6)	Strength: Control for confounding by logistic regression Weakness: Subjects not representative of general population

**Table II-10. Studies assessing the relationship between *Helicobacter pylori* infection and social factors**

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Buckley, 1998 <sup>72</sup>	Ireland	1000	Blood donors aged 18-60	HP prevalence – social class*: I/II (36.9%) III (44.0%) IV/V (50.0%) [p<0.01]	<b>Weakness:</b> No control for confounding; statistical test used unclear; non-representative population
Lin, 1998 <sup>73</sup>	Australia	273	General population Aged 20-80	Household income (increase in risk with decrease in income), OR=1.5 (1.1-2.4)	<b>Strength:</b> Population-based sample; control for confounding by logistic regression <b>Weakness:</b> Adjusted risks not presented for categorical data
Luzza, 1998 <sup>74</sup>	Rural Italy	705	Out-patients aged 1-87	<b>Nonmanual occupation:</b> OR=0.7 (0.5-0.9) <b>Childhood social class low:</b> HP+=54%, HP-=32%	<b>Strength:</b> Occupation controlled for confounding by logistic regression <b>Weakness:</b> Subjects not representative of general population; no control for confounding or statistical tests for childhood social class
Malaty, 1998 <sup>74</sup>	Sweden	270 twin pairs	Swedish Twin Registry adults, mean age=65.6	Crowded living conditions and poor economic conditions associated with HP+ in twins reared apart (p=0.02)	<b>Strength:</b> Study of twin pairs controlled for genetic effects <b>Weakness:</b> used paired t test – no adjustment for confounding
Rothenbacher, 1998 <sup>75</sup>	Germany	337	Adult students aged 50-80	<b>Education of father:</b> ≤9 years [referent] 10-11 years, OR=0.8 (0.5-1.5) ≥12 years, OR=0.4 (0.2-0.7)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Not representative of general population Note – UBT used
Souto, 1998 <sup>76</sup>	Brazil	184	General population aged 10-90	Annual family income – decrease in risk with increase in income [p for trend=0.013]	<b>Strength:</b> Population-based sample <b>Weakness:</b> No control for confounding

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Strachan, 1998 <sup>44</sup>	South Wales	1796	Population-based Prospective Heart Disease Study participants aged 45-59	HP prevalence - Social class at entry*: I/II (60.9%) IIINM (65.8%) IIIM (72.7%) IV/V (76.7%) [p<0.0001] Years of father's schooling ≤8, OR=1.2 (0.9-1.6)	Weakness: No control for confounding; statistical test used not specified
Stroffolini, 1998 <sup>46</sup>	Italy	1659	Military students		Strength: control for confounding by logistic regression Weakness: sample not representative of general population; sample may be too heterogeneous
Torres, 1998 <sup>48</sup>	Mexico	9116	General population aged 1-39	Education level College [referent] High school, OR=1.4 (1.2-1.8) Basic, OR=2.0 (1.6-2.4) Illiterate, OR=2.4 (1.7-3.4)	Strength: Sample representative of general population; age-adjusted ORs Weakness: no control for other confounding factors
Murray, 1997 <sup>41</sup>	Ireland	4742	General population sample aged 12-64 from electoral roll	HP prevalence - social class*: Increasing trend from I (43.0%) to V (68.1%) [p for trend>0.001] OR=2.8 (1.8-4.4) for V vs. I	Strength: Sample representative of general population; control for age and sex by logistic regression; Weakness: Possible bias from low response rate (58%)
Peach, 1997 <sup>43</sup>	Australia	217	General population sample from electoral roll	Negative HP status significantly associated with increasing education, OR=0.6 (0.4-1.0) [p<0.05]	Strength: Sample representative of general population; control for confounding by logistic regression
Rothenbacher, 1997 <sup>47</sup>	Germany	501	Out-patients	HP prevalence - school education: ≤9 years (30.5%) 10-11 years (20.5%) >12 years (14.4%) [p=0.051]	Weakness: Sample not representative of general population; no control for confounding except by age Note - UBT used

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Shinchi, 1997 <sup>34</sup>	Japan	566	Male self-defense officials aged 50-55	HP prevalence -- rank Low (82.5%) Middle (75.2%) High (75.0%) [p for trend=0.48]	<b>Weakness:</b> Sample not representative of general population; low serology specificity (76%); no control for confounding
Fraser, 1996 <sup>35</sup>	New Zealand	579	Workforce survey of subjects aged 40-64	The RR of HP infection for SES and Income were not statistically significant after adjusting for age and ethnicity (European, Maori, Pacific Islander). However, HP status varied with SES in Europeans: 1 & 2 [high] (21%) 3 (42%) 4 (45%) 5 & 6 [low] (54%) [p=0.011]	<b>Strength:</b> Presented RR estimates for SES in total group adjusted for age and ethnicity <b>Weakness:</b> Not representative of general population; SES in Europeans does not appear to be adjusted for age
Malaty, 1996 <sup>36</sup>	Korea	161 252	Volunteer Adults Children	<b>Adult social class, High [referent]</b> Middle, OR=1.0 (1.0-2.2) Low, OR=1.7 (1.7-18.0) <b>Child social class, High [referent]</b> Middle, OR=2.5 (1.1-5.5) Low, OR=5.2 (1.5-17.4)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Sample not representative of general population; over representation of middle class
Malaty, 1996 <sup>38</sup>	Russia	213 307	Adults Children Out-patients	<b>Income below the poverty level was associated with HP seroprevalence in children (OR=1.4, CI=1.2-2.5), but not in adults (OR=0.3, CI=0.2-0.8)</b>	<b>Strength:</b> Control for confounding by logistic regression for poverty level in adults <b>Weakness:</b> Subjects not representative of general population; control only for age in analysis of poverty level for children; Russian society is very homogeneous

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
McCallion, 1996 <sup>133</sup>	Ireland	367	3-15 year old outpatients	Social class – manual vs. nonmanual, OR=1.6 (1.0-2.6)	<b>Strength:</b> Control for confounding by logistic regression <b>Weakness:</b> Subjects not representative of general population
Staat, 1996 <sup>147</sup>	US	2581	6-19 year old participants in National survey	Income below poverty line, OR=1.5 (1.0-2.2) Head of household education level < 12 years, OR=1.8 (1.2-2.7)	<b>Strength:</b> Population-based sample; control for confounding by logistic regression
Chow, 1995 <sup>63</sup>	Australia	328	General population of Chinese immigrants aged >25	Years of education, $\geq 13$ [referent] 10-12, OR=2.1 7-9, OR=1.5 <7, OR=3.9 [p<0.001]	<b>Strength:</b> Subjects representative of general population <b>Weakness:</b> Adjusted ORs from logistic regression not presented
Gilboa, 1995 <sup>65</sup>	Rural Israel	377	General population sample aged 30-90	There was no difference in HP seroprevalence with educational level	<b>Strength:</b> Subjects representative of general population <b>Weakness:</b> ORs not presented; no control for confounding
Murray, 1995 <sup>66</sup>	Ireland	2115	Subjects aged 25-64 selected from General Practitioner lists	HP prevalence – social class*: I (38.0%) II (45.3%) IIINM (52.4%) IIIM (66.5%) IV (70.4%) V (66.0%)	<b>Strength:</b> Subjects representative of general population <b>Weakness:</b> ORs not presented; no control for confounding
Replogle, 1995 <sup>49</sup>	California	556	Health plan members aged 20-39	Years of education, < 12 [referent] 12, OR=0.6 (0.5-0.9) 12-16, OR=0.4 (0.3-0.5) >16, OR=0.3 (0.2-0.5)	<b>Strength:</b> Calculated RRs <b>Weakness:</b> Subjects not representative of general population; no control for confounding

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Malaty, 1994 <sup>77</sup>	Texas	150	Black & Hispanic healthy volunteers aged 19-49	Present social class not High, OR=2.2 (1.5-2.9) Childhood social class, High [referent] Middle, OR=8.9 (7.3-10.5) Low, OR=54.6 (52.7-56.5)	Strength: Control for confounding by logistic regression Weakness: Subjects not representative of general population
Teh, 1994 <sup>67</sup>	Taiwan	823	Children and Adults General population	Family income/month, ≤\$55 [referent] \$556-\$926, OR=1.0 (0.6-1.8) \$927-\$1481, OR=1.0 (0.6-1.8) >\$1482, OR=0.9 (0.5-1.7)	Strength: Subjects representative of general population; age-adjusted ORs Weakness: No control for other confounding factors
Webb, 1994 <sup>78</sup>	UK	471	Male volunteers	Manual occupation, OR=2.2 (1.1-4.6) Father manual occupation, OR=2.0 (0.9-4.9)	Strength: Control for confounding by logistic regression Weakness: Subjects not representative of general population
EUROGAST, 1993 <sup>68</sup>	17 Populations	3194	General population sample aged 25-34 and 55-64	Education level, Primary [referent] Secondary, OR=0.8 (0.6-1.0) Higher, OR=0.6 (0.4-0.8)	Strength: Subjects representative of general population; control for confounding by logistic regression
Hopkins, 1993 <sup>125</sup>	Chile	1815	General population <35 years of age	Low SES, OR=1.7 (1.3-2.1)	Strength: Subjects representative of general population; control for confounding by logistic regression
Malaty, 1992 <sup>79</sup>	Texas	108	Asymptomatic healthy Hispanic volunteers	Education level, College graduate [referent] High school graduate, OR=2.7 (1.6-12) Didn't graduate high school, OR=3.6 (1.8-9.7)	Strength: Control for confounding by logistic regression; study of risk factors in Hispanics Weakness: Subjects not representative of general population

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Mendall, 1992 <sup>100</sup>	UK	215	Subjects aged 18-82 attending a health-screening clinic	Current social class, I/II [referent] IIIM, OR=0.7 (0.3-2.1) IIIM, OR=2.2 (0.8-5.5) IV/V, OR=0.6 (0.2-1.7) [p for trend=0.9]	Strength: Control for confounding by logistic regression Weakness: Subjects not representative of general population
Graham, 1991 <sup>80</sup>	Texas Blacks Whites	246 239	Healthy volunteers aged 15-80	There was a significant inverse gradient between age-adjusted frequency of educational level and HP infection [p=0.001]	Strength: control for confounding by logistic regression Weakness: Subjects not representative of general population Note – UBT used

Social class – I=professional occupations, II=managerial occupations, III=skilled occupations (subdivided as nonmanual (NM) and manual (M)), IV=semiskilled occupations, and V=unskilled occupations



**Table II-11. Studies assessing the relationship between *Helicobacter pylori* infection and family history of gastric disease/ulcer**

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Brenner, 1998 <sup>155</sup>	Germany	863	Pre-school children out-patients	History of ulcer in mother, OR=11.7 (3.8-36.2) History of ulcer in father, OR=1.6 (0.4-5.5)	<b>Strength:</b> 79% participation rate; both variables controlled for confounding by logistic regression <b>Weakness:</b> mother's history only adjusted for age and sex
Elitsur, 1998 <sup>125</sup>	West Virginia	303	1-20 year old children attending hospitals/clinics	No difference in the percentage of HP+ (9.8%) and HP- (9.4%) children with a family history of peptic ulcer disease [p=0.86]	<b>Strength:</b> large study of children; controlled for confounding by multiple regression <b>Weakness:</b> Subjects not representative of "healthy" children; bias may have occurred in selection of participants; results hard to interpret
Kikuchi, 1998 <sup>17</sup>	Japan	4361	Public service workers	History of gastric disease in mother, OR=1.2 (0.9-1.7) History of gastric disease in father, OR=1.5 (1.2-1.8)	<b>Strength:</b> 87% participation rate; father's history controlled for confounding by logistic regression <b>Weakness:</b> mother's history only adjusted for age and sex
Breuer, 1996 <sup>73</sup>	Germany	260	Blood donors aged 18-61	Family history of ulcer, OR=1.3 (0.6-2.5)	<b>Strength:</b> All subjects approached participated <b>Weakness:</b> Subjects not representative of general population; no control for confounding
Martin-de-Argila, 1996 <sup>75</sup>	Spain	381	Healthy volunteers aged 5-77	Of those whose first degree relatives had peptic ulcer disease, 63%=HP+ and 37%=HP- [p=0.028]	<b>Weakness:</b> Sample not representative of general population; no control for confounding
Gasbarrini, 1995 <sup>64</sup>	San Marino	2237	General population sample aged 20-70+	History of ulcer in mother, OR=0.7 (0.5-1.1) History of ulcer in father, OR=1.2 (0.9-1.5) History of ulcer in sibling, OR=1.5 (1.1-2.1)	<b>Strength:</b> Subjects representative of general population; control for confounding by logistic regression

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Gilboa, 1995 <sup>65</sup>	Rural Israel	377	General population sample aged 30-90	No significant association between HP infection and family history of peptic ulcer	<b>Strength:</b> Subjects representative of general population <b>Weakness:</b> ORs not presented; no control for confounding

**Table II-12. Studies assessing the relationship between *Helicobacter pylori* infection and institutionalized populations**

<b>Author, Year, Ref No.</b>	<b>Country</b>	<b>No. in Study</b>	<b>Population</b>	<b>Outcome</b>	<b>Comments</b>
Kimura, 1999 <sup>98</sup>	Japan	196	Institutionalized neurologically impaired patients aged 3-64	Prevalence rate among institutionalized (81.1%) higher than healthy Japanese population or in home care patients with severe neurologic impairment (20%) [p,0.001]. Prevalence in inpatients increased with duration of institutionalization [p<0.01]. One year seroconversion rate=47.4%	<b>Weakness:</b> Prevalence rates not age-adjusted; no control for confounding
Bohmer, 1997 <sup>99</sup>	Netherlands	338	Institutionalized adults from 2 institutes for the intellectually disabled aged 11-89	Prevalence rate among institutionalized (82.8%) higher than Dutch population (approximately 50%) IQ<50, OR=1.9 (1.1-3.6) Rumination, OR=2.0, (1.1-3.6) Institutionalized longer than 15 years, OR=22 (3.9-128)	<b>Weakness:</b> Statistical tests used not specified; no apparent control for confounding
DeHert, 1997 <sup>100</sup>	Belgium	89 89	Institutionalized schizophrenic patients Volunteer blood donor controls	Prevalence of HP+ greater in patients (34.8%) than controls (14.6%), OR=3.0 (1.4-7.3) Prevalence in patients increased with length of stay in institution	<b>Strength:</b> Cases and controls matched for age and gender <b>Weakness:</b> Statistical tests used not specified; no apparent control for confounding; not clear if matched analysis was done Note – Letter to the Editor
Lewindon, 1997 <sup>101</sup>	Hong Kong	157 50	Institutionalized children aged 1-15 "Age-matched" out-patient controls	Prevalence of HP+ greater in patients (55.4%) than controls (8%) [p<0.0002]	<b>Weakness:</b> Mean age of in-patients 2.2 years older than mean age of out-patients; controls not representative of general population; statistical tests used not specified

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Breuer, 1996 <sup>33</sup>	Germany	260	Blood donors aged 18-61	Boarding school/orphanage during childhood, OR=2.6 (0.8-8.2)	<b>Strength:</b> All subjects approached participated <b>Weakness:</b> Subjects not representative of general population; no control for confounding; only 5% had not lived at home during childhood so power reduced
Malaty, 1996 <sup>34</sup>	Russia	307	1-19 year old children	Children from orphanages and communal apartments vs. those who have families, OR=2.1 (1.2-2.5)	<b>Weakness:</b> Subjects not representative of general population; control only for age;
Harris, 1995 <sup>31</sup>	UK	424 267	Adults residents of a hospital for people with severe learning difficulties Age-sex matched controls	Prevalence of HP+ greater in residents of hospital (87%) than in controls (41%) No differences in prevalence of HP+ for residents by age or duration of stay	<b>Weakness:</b> Controls not representative of general population; no control for confounding; not clear how age and sex controlled for in analysis since numbers of patients and controls varied by agegroup
Lambert, 1995 <sup>32</sup>	Australia	122 273	Institutionalized medically and physically handicapped young adults Population-based age-sex matched controls	Prevalence of HP+ greater in residents of hospital (75%) than in controls (23%), OR=13.4 (6.5-29) [p<0.001] Prevalence of HP+ greater in these same residents in 1989 (75%) than in 1977 (34%) after adjustment for age, OR=2.4 (1.1-5.3) [p<0.03] Duration of stay was significantly related to HP status in 1977, but not 1989 The annual seroconversion rate was 7.4%	<b>Strength:</b> Controls representative of general population; ORs adjusted for confounding by logistic regression <b>Weakness:</b> Not clear how age and sex controlled for in comparison of HP prevalence

**Table II-13. Studies assessing the relationship between *Helicobacter pylori* infection and familial exposures**

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Brenner, 1999 <sup>165</sup>	Germany	110	Employees of a health insurance company Their partners	Prevalence of HP+ greater in employees with HP+ partner (42%) than HP- partner (7%), OR=7.0 (CI=1.8-26.7) Risk increased with number of years lived with HP+ partner	<b>Strength:</b> Studied healthy employees not patients; controlled for confounding by logistic regression <b>Weakness:</b> No DNA fingerprinting; can't rule out common source of infection Note -- UBT used
Rothenbacher, 1999 <sup>163</sup>	Germany	1143	General population sample of first grade children	Risks for child being HP+ according to parental HP status: <b>Father HP+</b> , OR=3.8 (0.8-19.1) <b>Mother HP+</b> , OR=7.9 (4.0-15.7)	<b>Strength:</b> Representative sample of children; controlled for confounding by logistic regression <b>Weakness:</b> Data only available on one parent Note -- UBT used
Singh, 1999 <sup>164</sup>	India	25 25	General population subjects Married spouses	Prevalence of HP+ greater in spouses of HP+ subjects (83.3%) than HP- subjects (28.5%) [ $p<0.01$ ] 3 of 5 (60%) initially HP- spouses with HP+ spouses were HP+ at one year follow-up	<b>Strength:</b> Subjects selected from general population <b>Weakness:</b> No DNA fingerprinting; can't rule out common source of infection; no control for confounding Note -- biopsy, rapid urease test, histologic exam, and serology used
Brenner, 1998 <sup>155</sup>	Germany	863	Pre-school children out-patients	<b>History of ulcer in mother,</b> OR=11.7 (3.8-36.2) <b>History of ulcer in father,</b> OR=1.6 (0.4-5.5)	<b>Strength:</b> 79% participation rate; both variables controlled for confounding by logistic regression <b>Weakness:</b> mother's history only adjusted for age and sex; presence of ulcer used as surrogate for presence of HP infection
Chalkauskas, 1998 <sup>170</sup>	Lithuania	13 from 6 families	Dyspeptic patients and their relatives	Members of 2/6 families harbored same HP strain	<b>Strength:</b> Performed DNA fingerprinting <b>Weakness:</b> Can't rule out common source of infection

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Ma, 1998 <sup>103</sup>	China	49	General population sample Children 3-12	Risks for children being HP+ according to parental HP status - At least one parent HP+, OR=30.4 (4.0-232.2) <b>Father HP+</b> , OR=10.1 (1.6-63.2) <b>Mother HP+</b> , OR=30.1 (2.8-325.2) Risk for one spouse being HP+ when other spouse was HP+, OR=1.5 (0.6-3.7)	<b>Strength:</b> Representative sample of children; control for confounding by age and gender by logistic regression; bootstrap technique used to test differences between parents <b>Weakness:</b> small number of children; not total independence of children (7/41 had other sib participants); data not available on both mother and father for all 49 children; Note – UBT used for children
Bonamico, 1996 <sup>158</sup>	Italy	121 41	Relatives of HP+ children attending a pediatric clinic	Prevalence of HP+ in relatives of HP+ children (68%) was higher than in various control populations. The relative-specific prevalences were: mother (70%), father (67%), siblings (67%), other relative cohabitants (56%)	<b>Weakness:</b> No control group specific to study
Czkwianianc, 1996 <sup>150</sup>	Poland	240	Children aged 6 months-17 years who were patients at hospitals and clinics	Prevalence of HP+ higher in children who lived in households with HP seropositive relatives [p<0.005]	<b>Weakness:</b> Sample not representative of general population; no control for confounding; statistical tests not specified
Georgopoulos, 1996 <sup>166</sup>	Greece	64 64	Ulcer patients Spouses	Prevalence of HP+ greater in spouses of HP+ patients (78%) than HP- patients (20%), OR=14.0 (2.3-144.6) 8/18 couples colonized with identical HP strains	<b>Strength:</b> Chromosomal DNA from 18 couples analyzed <b>Weakness:</b> No control for confounding Note – biopsy, CLO, and culture used
Malaty, 1996 <sup>161</sup>	Russia	307	1-19 year old children	Child has HP+ siblings, OR=2.4 (2.1-2.7)	<b>Weakness:</b> Subjects not representative of general population; control only for age
Mitchell, 1996 <sup>169</sup>	Australia	3	Children	Twin boys and younger sister found to be infected with identical strains of HP	<b>Strength:</b> Analyzed antigen recognition pattern

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Parente, 1996 <sup>167</sup>	Italy	124 124 248	HP+ patients with ulcer Spouses Volunteer blood donors	Prevalence of HP+ greater in spouses of HP+ patients (71%) than in matched controls (58%) [p<0.05]	<b>Strength:</b> Control for confounding by logistic regression; spouses matched to controls by sex, age, area, SES <b>Weakness:</b> Controls not representative of general population
Schutze, 1995 <sup>168</sup>	Austria	18	Patients with chronic ulcer in whom HP had been eradicated	HP reinfection occurred in 2/18 patients by a HP strain identical to that carried by the spouse	<b>Strength:</b> Performed DNA fingerprinting <b>Weakness:</b> Can't rule out common source of infection
Blecker, 1994 <sup>169</sup>	Belgium	35	Family members of HP+ children	Prevalence of HP+ greater in family members of HP+ children (48.6%) compared to general population group (17.8%)	<b>Weakness:</b> Poor participation rate of families; lack of independence among members of same family; comparability regarding age of control population not known
Malaty, 1994 <sup>247</sup>	Sweden	269 twin pairs	Swedish Twin Registry adults, mean age=65.5	Variation in the acquisition of HP infection estimated to be 57% for genetic factors, 20% for shared environmental factors, and 23% for nonshared environmental factors	<b>Strength:</b> Intraclass correlations used to estimate influence of genetic and environmental effect in monozygotic and dizygotic twin pairs reared together and apart <b>Weakness:</b> Didn't assess specific risk factors
Barnford, 1993 <sup>248</sup>	Ireland	4 families	Parents of HP+ children	Members of 2 families harbored subtypes or strains of HP with the same DNA fingerprint	<b>Strength:</b> Performed DNA fingerprinting <b>Weakness:</b> Can't rule out common source of infection Note – biopsy and culture used
Mitchell, 1993 <sup>160</sup>	Austria	27 11 69	HP+ children HP- children Age-sex matched blood donors & children	Prevalence of HP+ greater in family members of HP+ children (76.7%) than HP- children (15%) and age-matched blood donor controls (21.7%) [p<0.001] Prevalence of HP+ greater in parents of HP+ children (81.1%) greater than in siblings (69.4%)	<b>Strength:</b> Compared HP+ prevalence in relatives of HP+ and HP- children as well as in age-sex matched controls <b>Weakness:</b> No control for other factors such as SES; lack of independence among members of same family

Author, Year, Ref No.	Country	No. in Study	Population	Outcome	Comments
Drum, 1990 <sup>61</sup>	Canada	67 22 37	Parents Siblings Child controls	Prevalence of HP+ greater in parents of HP+ children (73.5%) than HP- children (24.2%) Prevalence of HP+ greater in mothers of HP+ children (83.3%) than fathers (62.5%) Prevalence of HP+ greater in siblings of HP+ children (81.8%) than HP- children (2%) or similarly aged controls (14%)	<b>Strength:</b> Control for children from same hospital that served the patient and their siblings <b>Weakness:</b> No control for factors such as SES related to HP status



**Table IV-1. Distribution of cases and controls for selected variables by *Helicobacter pylori* serostatus**

Factors	<u><i>H. pylori</i> +</u>		<u><i>H. pylori</i> -</u>		<u>Indeterminate</u>	
	N 1994	(col%) (row%)	N 1019	(col%) (row%)	N 275	(col%) (row%)
<u>Age in Years</u>						
<40	484	(24) (63)	219	(21.5) (28)	67	(24) (9)
40-44	530	(27) (62.5)	250	(24.5) (29)	68	(25) (8)
45-54	537	(27) (60)	290	(28) (32)	66	(24) (7)
55-59	170	(8.5) (57)	102	(10) (34)	27	(10) (9)
60+	273	(14) (57)	158	(15.5) (33)	47	(17) (10)
<u>Gender</u>						
Male	978	(49) (59)	536	(53) (32)	155	(56) (9)
Female	1016	(51) (63)	483	(47) (30)	120	(44) (7)
<u>Grouped Gastric Pathology Categories</u>						
Normal, SG	21	(1) (28)	47	(5) (64)	6	(2) (8)
CAG (III) mild	546	(27) (46)	523	(51) (45)	104	(38) (9)
Other CAG	188	(9) (77)	37	(4) (15)	19	(7) (8)
IM supperficial	183	(9) (67)	71	(7) (26)	21	(8) (8)
IM deep	656	(33) (71)	190	(19) (21)	78	(28) (8)

Factors	<u><i>H. pylori</i> +</u>		<u><i>H. pylori</i> -</u>		<u>Indeterminate</u>	
	N 1994	(col%) (row%)	N 1019	(col%) (row%)	N 275	(col%) (row%)
Dysplasia	298	(15) (68)	105	(10) (24)	34	(12) (8)
Cancer	4	(0.2) (80)	1	(0.1) (20)	0	---
Missing	98	(5) (63)	45	(4) (29)	13	(5) (8)
<u>Village name</u>						
Xi Quan	155	(8) (67)	52	(5) (22)	26	(9) (9)
Li Hu Zhuang	133	(7) (56)	81	(5) (34)	25	(9) (11)
Wang Jia Zhuang	183	(9) (76)	44	(4) (18)	13	(5) (5)
Xi Si Hou	61	(3) (56)	39	(4) (36)	9	(3) (8)
Li Jia Gou	215	(11) (67)	85	(8) (26)	22	(8) (7)
Suo Zhuang	246	(12) (64)	101	(10) (26)	40	(14.5) (10)
Huang Ai Quad	125	(6) (75)	32	(3) (19)	9	(3) (5)
Yang Jia He	182	(9) (71)	60	(6) (23)	14	(5) (5)
Xin Zhuang	140	(7) (50)	114	(11) (41)	25	(9) (9)
Guo Jia Zhuang	160	(8) (47)	152	(15) (44)	32	(12) (9)
Hou Jia He	214	(11) (55)	146	(14) (37)	31	(11) (8)

Factors	<b><i>H. pylori</i> +</b>		<b><i>H. pylori</i> -</b>		<b>Indeterminate</b>	
	N 1994	(col%) (row%)	N 1019	(col%) (row%)	N 275	(col%) (row%)
Hou He Ye	87	(4) (49)	71	(7) (40)	19	(7) (11)
Nan Yang He	93	(5) (64)	42	(4) (29)	10	(4) (7)

**Table IV-2. Association between prevalence of *Helicobacter pylori* infection and cigarette smoking**

<b>Smoking Category</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a,b</sup></b>	<b>95% CI</b>	<b>95% CI<sup>c</sup></b>
<u>Smoked cigarettes</u>					
Never	1166	553	1.0	---	---
Ever	828	466	0.9	0.7-1.0	0.7-1.0
<u>Age first started smoking</u>					
<18	142	96	0.7	0.5-0.9	0.5-0.9
18-20	329	164	1.0	0.8-1.2	0.8-1.2
21-25	170	102	0.8	0.6-1.0	0.6-1.0
>25	187	104	0.9	0.7-1.2	0.7-1.2
<u>Number smoked per day</u>					
<10	169	93	0.9	0.7-1.2	0.7-1.1
10-19	174	92	0.9	0.7-1.2	0.7-1.2
20	338	205	0.8	0.6-1.0	0.6-1.0
>20	146	76	0.9	0.7-1.2	0.7-1.2
<u>Number of years smoked</u>					
<20	180	105	0.8	0.6-1.0	0.6-1.0
20-24	186	85	1.0	0.8-1.3	0.8-1.3
25-29	147	80	0.9	0.6-1.2	0.6-1.2
30-39	182	114	0.8	0.6-1.0	0.6-1.0
>39	133	82	0.9	0.6-1.2	0.6-1.2
<u>Lifetime packs of cigarettes smoked</u>					
<3595	164	95	0.8	0.6-1.1	0.7-1.0
3595-6862	176	79	1.1	0.8-1.4	0.8-1.4
6863-9490	181	98	0.9	0.7-1.1	0.7-1.1
9491-14235	152	100	0.7	0.6-1.0	0.6-1.0
>14235	154	94	0.8	0.6-1.1	0.6-1.1

<b>Smoking Category</b>	<b>Positivee</b>	<b>Negative</b>	<b>OR<sup>a,b</sup></b>	<b>95% CI</b>	<b>95% CI<sup>c</sup></b>
<u>Smoking status</u>					
Current	749	420	0.9	0.7-1.0	0.7-1.0
Past	79	46	0.8	0.6-1.2	0.6-1.3

<sup>a</sup>Those who never smoked cigarettes were referent category for all OR calculated.

<sup>b</sup>Adjusted for age in a polychotomous logistic model.

<sup>c</sup>Calculated using bootstrap technique.

**Table IV-3. Association between prevalence of *Helicobacter pylori* infection and alcoholic beverage consumption**

<b>Drinking Category</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a,b</sup></b>	<b>95% CI</b>	<b>95% CI<sup>c</sup></b>
<u>Drank alcohol</u>					
Never	1092	548	1.0	---	---
Ever	902	471	1.0	0.8-1.1	0.8-1.1
<u>Age first started drinking</u>					
<18	151	73	1.0	0.8-1.4	0.8-1.4
18-20	345	175	1.0	0.8-1.2	0.8-1.2
21-25	166	102	0.8	0.6-1.0	0.6-1.0
>25	240	121	1.0	0.8-1.3	0.8-1.3
<u>Number of times drank per week</u>					
<3	217	102	1.0	0.8-1.3	0.8-1.4
3-6	229	119	1.0	0.7-1.2	0.7-1.2
7-9	271	146	0.9	0.8-1.2	0.7-1.2
>9	183	104	0.9	0.7-1.2	0.7-1.2
<u>Number of years drank</u>					
<20	262	96	1.3	1.0-1.7	1.0-1.6
20-24	198	112	0.8	0.7-1.1	0.6-1.1
25-34	271	171	0.8	0.6-1.0	0.6-1.0
>34	171	92	1.0	0.8-1.4	0.8-1.4
<u>Drinking status</u>					
Current	843	446	0.9	0.8-1.1	0.8-1.1
Past	59	25	1.2	0.8-2.0	0.8-1.9

<sup>a</sup>Those who never drank were referent category for all OR calculated.

<sup>b</sup>Adjusted for age in a polychotomous logistic model.

<sup>c</sup>Calculated using bootstrap technique.

**Table IV-4. Association between prevalence of *Helicobacter pylori* infection and dietary variables**

<b>Dietary Variables</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95%CI</b>	<b>95%CI<sup>b</sup></b>
<u>Jin<sup>c</sup> of garlic eaten per year</u>					
<2	420	212	1.0	---	---
2	351	162	1.1	0.8-1.4	0.8-1.4
3-4	349	156	1.1	0.8-1.4	0.8-1.4
5	274	163	0.8	0.6-1.1	0.6-1.1
>5	321	175	0.9	0.7-1.2	0.7-1.2
<u>Jin<sup>c</sup> of garlic stalk eaten per year</u>					
0	495	216	1.0	---	---
1	206	89	1.0	0.7-1.3	0.7-1.3
2	394	227	0.7	0.6-0.9	0.6-0.9
3-4	284	148	0.8	0.6-1.1	0.6-1.0
>4	336	188	0.8	0.6-1.0	0.6-1.0
<u>Jin<sup>c</sup> of scallions eaten per year</u>					
<3	352	130	1.0	---	---
3-4	267	135	0.7	0.5-1.0	0.6-0.9
5-7	433	256	0.6	0.5-0.8	0.5-0.8
8-10	411	227	0.7	0.5-0.9	0.5-0.9
>10	252	120	0.8	0.6-1.0	0.6-1.1
<u>Jin<sup>c</sup> of chives eaten per year</u>					
<3	353	178	1.0	---	---
3-4	199	101	1.0	0.7-1.3	0.7-1.3
5-7	442	249	0.9	0.7-1.1	0.7-1.1
8-10	460	225	1.0	0.8-1.3	0.8-1.2
>10	261	115	1.1	0.8-1.5	0.8-1.5

<b>Dietary Variables</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95%CI</b>	<b>95%CI<sup>b</sup></b>
<u>Jin<sup>c</sup> of allium vegetables eaten per year</u>					
<11	354	161	1.0	---	---
11-15	342	172	0.9	0.7-1.1	0.7-1.1
16-21	339	173	0.9	0.7-1.1	0.6-1.2
22-30	361	195	0.8	0.6-1.1	0.6-1.0
>30	319	167	0.8	0.6-1.1	0.7-1.1
<u>Number of times per month ate raw fruits and vegetables</u>					
Never ate	103	54	1.0	---	---
Ever ate	1891	964	1.0	0.7-1.4	0.7-1.4
<3	296	150	1.0	0.7-1.5	0.7-1.5
3-5.9	391	222	0.9	0.6-1.3	0.6-1.3
6-9.9	408	219	0.9	0.6-1.3	0.6-1.4
10-15.9	438	201	1.1	0.7-1.6	0.7-1.6
≥16	358	172	1.0	0.7-1.5	0.7-1.5
<u>Frequency washed their raw fruits and vegetables</u>					
Always	1179	553	1.0	---	---
> half the time	386	215	0.8	0.7-1.0	0.7-1.0
< half the time	249	141	0.8	0.6-1.0	0.6-1.0
Never	77	56	0.7	0.5-1.0	0.5-0.9
<u>Frequency peeled their raw fruits and vegetables</u>					
Always	314	174	1.0	---	---
> half the time	252	105	1.3	1.0-1.7	0.9-1.8
< half the time	309	162	1.0	0.8-1.3	0.7-1.4
Never	1016	524	1.0	0.8-1.3	0.8-1.3
<u>Lian<sup>d</sup> of sour pancakes eaten per year</u>					
Never ate	1493	791	1.0	---	---
Ever ate	501	228	1.1	1.0-1.4	0.9-1.4
<271	166	79	1.1	0.8-1.5	0.8-1.5
271-900	166	75	1.1	0.9-1.5	0.8-1.6
>900	168	73	1.2	0.9-1.6	0.8-1.7



<b>Dietary Variables</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95%CI</b>	<b>95%CI<sup>b</sup></b>
<u>Lian<sup>d</sup> of sweet pancakes eaten per year</u>					
Never ate	1005	464	1.0	---	---
Ever ate	989	555	0.8	0.7-0.9	0.7-0.9
<225	337	174	0.9	0.7-1.1	0.7-1.1
225-525	322	194	0.7	0.6-0.9	0.6-0.9
>525	330	186	0.8	0.6-1.0	0.6-1.0
<u>Preferred saltiness of food</u>					
Lightly salty	419	239	1.0	---	---
Moderately salty	415	205	1.1	0.9-1.4	0.9-1.5
Very salty	1160	575	1.1	0.9-1.3	0.9-1.4

<sup>a</sup>Adjusted for age in a polychotomous logistic model.

<sup>b</sup>Calculated using bootstrap technique.

<sup>c</sup>1 jin ~ 500 grams.

<sup>d</sup>1 lian ~ 50 grams.

**Table IV-5. Association between prevalence of *Helicobacter pylori* infection and occupation variables**

<b>Occupation<sup>a</sup></b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>b,c</sup></b>	<b>95% CI</b>	<b>95% CI<sup>d</sup></b>
Administrative	112	56	1.0	0.7-1.4	0.7-1.3
Technical/clerical/sales	16	10	0.8	0.4-1.7	0.3-2.0
Precision production	62	22	1.4	0.8-2.2	0.8-2.2
Operator/fabricator/laborer	28	21	0.7	0.4-1.2	0.3-1.2
Service occupations	427	201	1.2	1.0-1.4	0.9-1.4
Farming	1505	764	1.0	0.8-1.2	0.8-1.1
Animal worker	9	11	0.5	0.2-1.1	0.2-1.2

<sup>a</sup>The number of subjects obtained by summing all occupations exceeds the total number of subjects in the study since some subjects reported having more than one occupation.

<sup>b</sup>Those not employed in each occupation are the referent group for each occupation.

<sup>c</sup>Adjusted for age in a polychotomous logistic model.

<sup>d</sup>Calculated using bootstrap technique.

**Table IV-6. Association between prevalence of *Helicobacter pylori* infection and water-related exposures**

<b>Water Variables</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95% CI</b>	<b>95% CI<sup>b</sup></b>
<u>Source of drinking water</u>					
Deep private well	235	163	1.0	---	---
Shallow private well	1004	543	1.3	1.0-1.6	1.0-1.7
Deep village well	70	35	1.4	0.9-2.2	0.8-2.3
Shallow village well	648	250	1.8	1.4-2.3	1.4-2.3
Pond/river/ditch	25	22	0.8	0.4-1.5	0.4-1.5
Running/spring water	12	6	1.4	0.5-3.8	0.6-3.4
<u>Number of days store drinking water in a jar</u>					
None	496	225	1.0	---	---
Some	1498	794	0.9	0.7-1.0	0.7-1.0
<3	538	271	0.9	0.7-1.1	0.7-1.1
3	338	186	0.8	0.7-1.1	0.7-1.1
>3	621	337	0.8	0.7-1.0	0.7-1.0
<u>Frequency that water is boiled</u>					
Always	1372	704	1.0	---	---
Often	511	255	1.0	0.8-1.2	0.8-1.2
Sometimes	77	33	1.1	0.8-1.7	0.7-1.8
Never	33	26	0.7	0.4-1.1	0.4-1.1
<u>Location washed diapers</u>					
Never washed diapers	634	360	1.0	---	---
Washed in house	574	294	1.1	0.9-1.3	0.9-1.3
Washed in river/stream	941	430	1.2	1.0-1.5	1.0-1.4
Washed in pond/ditch	12	3	2.2	0.6-7.8	NA <sup>c</sup>

<b>Water Variables</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95% CI</b>	<b>95% CI<sup>b</sup></b>
<u>Location washed/bathed when weather was warm</u>					
Never washed	218	146	1.0	---	---
Ever washed	1776	873	1.3	1.0-1.6	1.0-1.6
Washed at home	616	298	1.3	1.0-1.7	1.0-1.7
Washed in court yard	572	292	1.2	1.0-1.6	1.0-1.5
Washed in stream	521	270	1.2	1.0-1.6	1.0-1.6
Washed in pond/ditch	108	43	1.6	1.0-2.4	1.0-2.4
Washed in public bath	18	4	2.8	0.9-8.4	NA <sup>c</sup>
<u>Number of times per month washed/bathed when weather was warm</u>					
Never washed	218	146	1.0	---	---
1-4	511	261	1.3	1.0-1.6	1.0-1.7
4.1-8.0	391	180	1.4	1.0-1.8	1.0-1.8
8.1-25.9	479	226	1.3	1.0-1.8	1.0-1.8
≥26	395	206	1.2	0.9-1.6	0.9-1.7
<u>Washed/ bathed when weather was cold</u>					
No	1767	919	1.0	---	---
Yes	227	100	1.1	0.9-1.5	0.9-1.5
<u>Number of times per year swim in river/reservoir</u>					
None	130	352	1.0	---	---
Some	135	267	1.0	0.7-1.4	0.7-1.4
1-4	61	34	0.9	0.6-1.3	0.6-1.3
>4	62	25	1.2	0.8-1.9	0.7-2.0

<sup>a</sup>Adjusted for age in a polychotomous logistic model.

<sup>b</sup>Calculated using bootstrap technique.

<sup>c</sup>Not available - does not meet asymptotic assumption for bootstrap technique.

**Table IV-7. Association between prevalence of *Helicobacter pylori* infection and animals and pets**

<b>Animal Variables</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95%CI</b>	<b>95%CI<sup>b</sup></b>
<u>Number of animals kept in the house as an adult</u>					
No animals	1897	947	1.0	---	---
Some animals	96	72	0.7	0.5-0.9	0.5-1.0
1	38	37	0.5	0.3-0.8	0.3-0.9
2-4	22	13	0.9	0.4-1.7	0.4-1.7
>4	33	19	0.9	0.5-1.6	0.5-1.7
<u>Types of animals kept in the house as an adult</u>					
No animals	1897	947	1.0	---	---
Cats	33	27	0.6	0.4-1.0	0.3-1.1
Dogs	7	3	1.2	0.3-4.5	NA <sup>c</sup>
Rabbits	47	34	0.7	0.4-1.1	0.4-1.1
<u>Types of animals kept in the courtyard as an adult</u>					
No animals	62	27	1.0	---	---
Some animals	1932	992	0.8	0.5-1.3	0.5-1.2
Cats	26	15	0.7	0.3-1.5	0.3-1.6
Chickens	1617	856	0.8	0.5-1.2	0.4-1.4
Cows	307	189	0.6	0.4-1.1	0.4-1.1
Dogs	365	164	0.9	0.6-1.5	0.6-1.5
Donkeys	68	40	0.7	0.4-1.3	0.4-1.3
Ducks	956	502	0.8	0.5-1.2	0.5-1.3
Geese	253	145	0.7	0.4-1.2	0.4-1.2
Goats	488	242	0.8	0.5-1.4	0.5-1.4
Pigs	1469	759	0.8	0.5-1.2	0.5-1.2
Rabbits	346	180	0.8	0.5-1.3	0.5-1.4
Sheep	2	3	0.3	0.04-1.7	NA <sup>c</sup>

<b>Animal Variables</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95%CI</b>	<b>95%CI<sup>b</sup></b>
<u>Number of animals kept in the house at age 10</u>					
No animals	1677	853	1.0	---	---
Some animals	312	159	1.0	0.8-1.2	0.8-1.2
1	71	49	0.7	0.5-1.0	0.5-1.1
2-4	97	43	1.1	0.8-1.6	0.7-1.6
>4	131	56	1.1	0.8-1.6	0.8-1.5
<u>Types of animals kept in the house at age 10</u>					
No animals	1677	853	1.0	---	---
Cats	70	52	0.7	0.5-1.0	0.5-1.0
Dogs	18	17	0.5	0.3-1.0	0.3-1.0
Rabbits	76	59	1.1	0.9-1.5	0.9-1.4
<u>Had job working with animals</u>					
No	1981	1006	1.0	---	---
Yes	9	11	0.5	0.2-1.1	0.2-1.2

<sup>a</sup>Adjusted for age in a polychotomous logistic model.

<sup>b</sup>Calculated using bootstrap technique.

<sup>c</sup>Not available - does not meet asymptotic assumption for bootstrap technique.

**Table IV-8. Association between prevalence of *Helicobacter pylori* infection and hygiene factors**

<b>Hygiene factors</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95% CI</b>	<b>95% CI<sup>b</sup></b>
<u>Number of times per month spit onto the ground</u>					
Never spit	695	331	1.0	---	---
Ever spit	1298	687	0.9	0.8-1.1	0.8-1.0
<30	278	152	0.9	0.7-1.1	0.7-1.1
30-89	289	158	0.9	0.7-1.1	0.7-1.1
90-180	463	233	0.9	0.8-1.2	0.8-1.2
>180	268	144	0.9	0.7-1.1	0.7-1.1
<u>Number of times per month brushed teeth</u>					
Never brushed	1197	628	1.0	---	---
Ever brushed	797	390	1.0	0.9-1.2	0.8-1.3
<6	229	110	1.0	0.8-1.3	0.8-1.3
6-15	302	163	0.9	0.7-1.1	0.7-1.1
>15	266	117	1.1	0.9-1.4	0.9-1.5
<u>Frequency of hand washing before eating meals</u>					
Always	1689	867	1.0	---	---
> half the time	237	130	1.0	0.8-1.2	0.7-1.2
< half the time	61	21	1.6	1.0-2.6	1.0-2.5
Never	7	1	3.8	0.5-31.0	NA <sup>c</sup>
<u>Frequency of hand washing after bowel movements</u>					
Always	961	427	1.0	---	---
> half the time	493	294	0.7	0.6-0.9	0.6-0.9
< half the time	333	187	0.8	0.7-1.0	0.7-1.0
Never	207	111	0.9	0.7-1.1	0.7-1.1
<u>Frequency of hand washing before preparing meals</u>					
Always	1299	645	1.0	---	---
> half the time	88	48	0.9	0.7-1.3	0.6-1.4
< half the time	30	13	1.2	0.6-2.3	0.6-2.2
Never	6	5	0.6	0.2-2.0	0.2-2.2

<b>Hvgiene factors</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95% CI</b>	<b>95% CI<sup>b</sup></b>
<u>Frequency of hand washing with soap</u>					
Always	706	338	1.0	---	---
> half the time	518	270	0.9	0.8-1.1	0.8-1.1
< half the time	591	315	0.9	0.8-1.1	0.8-1.1
Never	179	96	0.9	0.7-1.2	0.7-1.2
<u>Frequency of body washing with soap</u>					
Always	814	387	1.0	---	---
> half the time	265	142	0.9	0.7-1.1	0.7-1.1
< half the time	270	122	1.1	0.8-1.4	0.8-1.4
Never	426	221	1.0	0.8-1.2	0.8-1.2
<u>Frequency of washing chopsticks and bowls</u>					
Always	1928	982	1.0	---	---
> half the time	59	32	0.9	0.6-1.5	0.6-1.4
< than half the time	5	5	0.5	0.2-1.9	NA <sup>c</sup>
Never	2	0	---	---	---
<u>Frequency of washing chopsticks and bowls with detergent</u>					
Always	29	12	1.0	---	---
> half the time	25	10	1.0	0.4-2.8	0.4-3.0
< half the time	253	127	0.8	0.4-1.7	0.4-1.7
Never	1686	868	0.8	0.4-1.6	0.4-1.6
<u>Temperature of water used to wash chopsticks and bowls</u>					
Hot	13	7	1.0	---	---
Cold	1861	963	1.3	0.5-3.4	0.4-4.2
Both	120	49	1.0	0.4-2.5	0.3-3.2
<u>Frequency of cup washing after use</u>					
Always	1800	901	1.0	---	---
> half the time	109	78	0.7	0.5-0.9	0.5-0.9
< half the time	66	29	1.1	0.7-1.8	0.7-1.9
Never	19	11	0.9	0.4-1.9	0.4-2.0



<b>Hvgiene factors</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95% CI</b>	<b>95% CI<sup>b</sup></b>
<u>Frequency of sharing cups with family</u>					
Always	1847	915	1.0	---	---
> half the time	31	19	0.9	0.5-1.5	0.4-1.8
< half the time	24	23	0.6	0.3-1.0	0.3-1.1
Never	92	62	0.8	0.6-1.1	0.6-1.1
<u>Frequency of pre-chewing child's food</u>					
Always	853	413	1.0	---	---
Sometimes	251	110	1.1	0.8-1.4	0.8-1.4
Never	890	496	0.9	0.7-1.0	0.7-1.0
<u>Frequency of kissing young (&lt; age 10) children on the lips</u>					
Always	381	172	1.0	---	---
Sometimes	625	327	0.9	0.7-1.1	0.7-1.1
Never	988	520	0.9	0.7-1.1	0.7-1.1
<u>Frequency of parents pre-chewing your food as a child</u>					
Always	1588	803	1.0	---	---
Sometimes	61	29	1.1	0.7-1.7	0.7-1.7
Never	89	56	0.8	0.6-1.1	0.6-1.1
<u>Frequency of parents kissing you on the lips as a child</u>					
Always	388	187	1.0	---	---
Sometimes	407	198	1.0	0.8-1.3	0.8-1.2
Never	458	251	0.9	0.7-1.1	0.7-1.1
<u>Type of flooring in house at age 10</u>					
Ground	1979	1009	1.0	---	---
Brick	11	8	0.7	0.3-1.9	0.3-2.2
Cement	2	2	0.5	0.1-3.8	NA <sup>c</sup>
Wood	1	0	~	---	---

<sup>a</sup>Adjusted for age in a polychotomous logistic model.

<sup>b</sup>Calculated using bootstrap technique.

<sup>c</sup>Not available - does not meet asymptotic assumption for bootstrap technique.

**Table IV-9. Association between prevalence of *Helicobacter pylori* infection and density/crowding factors**

<b>Hvgiene factors</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95% CI</b>	<b>95% CI<sup>b</sup></b>
<u>Number of people in household as an adult</u>					
<3	407	228	1.0	---	---
3	269	132	1.0	0.8-1.4	0.7-1.4
4	662	342	0.9	0.7-1.2	0.6-1.2
5	454	223	1.0	0.7-1.3	0.7-1.3
>5	201	94	1.0	0.7-1.4	0.7-1.5
<u>Number of children in household as an adult</u>					
0	1458	767	1.0	---	---
1	402	196	1.0	0.9-1.3	0.8-1.3
>1	55	14	2.0	1.1-3.6	1.0-3.7
<u>Number of people shared a bed with as an adult</u>					
0	283	166	1.0	---	---
1	1309	640	1.1	0.9-1.4	0.9-1.4
2	254	150	0.9	0.7-1.2	0.6-1.2
>2	67	17	2.1	1.2-3.7	1.1-3.8
<u>Number of children shared a bed with as an adult</u>					
Never shared a bed	283	166	1.0	---	---
Shared with child	429	232	1.0	0.8-1.3	0.7-1.3
1	337	199	0.9	0.7-1.2	0.7-1.2
>1	82	25	1.7	1.0-2.8	1.0-2.8
Shared bed with adult	1203	579	1.2	0.9-1.4	0.9-1.4
<u>Shared a bed with spouse as an adult</u>					
Never shared a bed	283	166	1.0	---	---
Yes	1513	741	1.1	0.9-1.4	0.9-1.4
No	119	70	0.9	0.7-1.3	0.7-1.3

<b>Hygiene factors</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95% CI</b>	<b>95% CI<sup>b</sup></b>
<u>Number of people in household when 10 years old</u>					
<5	339	153	1.0	---	---
5	377	197	0.8	0.7-1.1	0.6-1.1
6	460	237	0.8	0.6-1.1	0.6-1.1
7	363	207	0.7	0.6-1.0	0.6-1.0
>7	452	225	0.8	0.7-1.1	0.7-1.1
<u>Number of siblings less than 5 years old in household when subject was 10</u>					
No siblings <5	739	366	1.0	---	---
Yes siblings <5	1150	599	0.9	0.8-1.1	0.8-1.1
1	672	372	0.9	0.7-1.1	0.7-1.1
2	426	208	1.0	0.8-1.2	0.8-1.2
>2	44	15	1.4	0.8-2.5	0.8-2.6
No siblings	88	41	1.1	0.8-1.7	0.7-1.7
<u>Number of siblings less than 10 years old in household when subject was 10</u>					
No siblings <10	372	187	1.0	---	---
Yes siblings <10	1522	783	1.0	0.8-1.2	0.8-1.2
1	514	267	1.0	0.8-1.2	0.7-1.1
2	546	309	0.9	0.7-1.1	0.8-1.2
>2	449	201	1.1	0.8-1.4	0.8-1.4
No siblings	88	41	1.1	0.8-1.7	0.8-1.7
<u>Number of people shared a bed with at age 10</u>					
None	106	46	1.0	---	---
1	516	228	1.0	0.7-1.4	0.6-1.5
2-3	663	358	0.8	0.6-1.2	0.5-1.2
4	296	164	0.8	0.5-1.2	0.5-1.2
>4	406	218	0.8	0.6-1.2	0.5-1.2

<b>Hygiene factors</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95% CI</b>	<b>95% CI<sup>b</sup></b>
<u>Number of people shared a bed with at age 5</u>					
<2	314	128	1.0	---	---
2	437	227	0.8	0.6-1.0	0.6-1.0
3	506	281	0.7	0.6-0.9	0.5-1.0
4	341	186	0.7	0.6-1.0	0.6-1.0
>4	249	127	0.8	0.6-1.1	0.6-1.1

<sup>a</sup>Adjusted for age in a polychotomous logistic model.

<sup>b</sup>Calculated using bootstrap technique.

**Table IV-10. Association between prevalence of *Helicobacter pylori* infection and social factors**

<b>Social factors</b>	<b>Positive</b>	<b>Negative</b>	<b>ORa</b>	<b>95% CI</b>	<b>95% CI<sup>b</sup></b>
<u>Marital status</u>					
Married	1831	921	1.0	---	---
Widowed	146	78	1.1	0.8-1.4	0.8-1.5
Divorced or	2	3	0.4	0.06-2.2	NA <sup>c</sup>
Never married	15	17	0.4	0.2-0.9	0.2-0.9
<u>Number of years of subject's education</u>					
<1	693	349	1.0	---	---
1-3	358	193	0.9	0.7-1.1	0.7-1.2
4-6	522	254	1.0	0.8-1.2	0.8-1.2
7-9	356	196	0.8	0.6-1.0	0.6-1.1
>9	65	27	1.1	0.7-1.8	0.7-1.8
<u>Number of years of spouse's education</u>					
<1	584	324	1.0	---	---
1-3	323	168	1.0	0.8-1.3	0.8-1.3
4-6	484	219	1.2	0.9-1.4	0.9-1.4
7-9	389	175	1.1	0.9-1.4	0.9-1.4
>9	45	32	0.7	0.4-1.1	0.4-1.1
<u>Village education level</u>					
High	448	376	1.0	---	---
Medium	768	374	1.7	1.4-2.1	1.4-2.1
Low	778	269	2.4	2.0-2.9	2.0-3.0

<b>Social factors</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95% CI</b>	<b>95% CI<sup>b</sup></b>
<u>Subject's annual income in Yuan<sup>d</sup></u>					
<2,000	330	183	1.0	---	---
2,000-3,999	555	264	1.1	0.8-1.3	0.8-1.3
4,000-5,999	421	225	0.9	0.7-1.2	0.7-1.2
6,000-7,999	269	156	0.8	0.6-1.1	0.6-1.1
>8,000	412	189	1.0	0.8-1.4	0.8-1.4

<sup>a</sup>Adjusted for age in a polychotomous logistic model.

<sup>b</sup>Calculated using bootstrap technique.

<sup>c</sup>Not available using bootstrap technique.

<sup>d</sup>10 yuan ~ \$1.25 U.S.

**Table IV-11. Association between prevalence of *Helicobacter pylori* infection and gastric factors**

<b>Gastric factors</b>	<b>Positive</b>	<b>Negative</b>	<b>OR<sup>a</sup></b>	<b>95% CI</b>	<b>95% CI<sup>b</sup></b>
<u>Number of times per month have gastric reflux</u>					
Never	1089	555	1.0	---	---
Ever	901	464	1.0	0.8-1.1	0.8-1.1
<0.43	300	156	1.0	0.8-1.2	0.8-1.2
0.43-3.9	357	165	1.1	0.9-1.3	0.9-1.3
4.0-8.9	117	63	0.9	0.7-1.3	0.7-1.4
>9	127	80	0.8	0.6-1.1	0.6-1.1

<sup>a</sup>Adjusted for age in a polychotomous logistic model.

<sup>b</sup>Calculated using bootstrap technique.

**Table IV-12. Prevalence rate, prevalence rate ratio, and relative odds ratio of *Helicobacter pylori* infection for combinations of models according to age, percent of time washed hands before eating, number of children in the household, and village education level**

Age	% Wash Hands	# Children in House	Village Education	Prevalence Rate	Prevalence Rate Ratio <sup>a</sup>	Relative Odds Ratio <sup>b</sup>
40	<50%	2+	low	74 (59-86)	1.4 (1.1-1.7)	8.6 (3.9-22.2)
40	>50%	2+	low	75 (64-84)	1.5 (1.2-1.7)	5.0 (2.7-10.7)
40	<50%	0-1	low	74 (66-83)	1.5 (1.3-1.7)	4.1 (2.5-7.8)
40	>50%	0-1	low	70 (67-72)	1.4 (1.3-1.5)	2.4 (2.0-3.0)
40	<50%	2+	med	70 (54-83)	1.4 (1.1-1.7)	6.0 (2.7-16.2)
40	>50%	2+	med	69 (58-79)	1.4 (1.1-1.6)	3.5 (1.9-7.4)
40	<50%	0-1	med	69 (59-78)	1.4 (1.2-1.6)	2.8 (1.7-5.2)
40	>50%	0-1	med	63 (60-66)	1.2 (1.1-1.3)	1.7 (1.4-2.0)
40	<50%	2+	high	61 (43-77)	1.2 (0.9-1.5)	3.6 (1.6-9.3)
40	>50%	2+	high	60 (47-72)	1.2 (0.9-1.4)	2.1 (1.2-4.4)
40	<50%	0-1	high	59 (48-70)	1.2 (0.9-1.4)	1.7 (1.1-3.1)
40	>50%	0-1	high	51 (47-55)	1.0	1.0
50	<50%	2+	low	72 (57-85)	1.5 (1.1-1.8)	8.6 (3.9-22.2)
50	>50%	2+	low	73 (62-82)	1.5 (1.3-1.7)	5.0 (2.7-10.7)
50	<50%	0-1	low	73 (64-81)	1.5 (1.3-1.7)	4.1 (2.5-7.8)
50	>50%	0-1	low	68 (65-70)	1.4 (1.3-1.5)	2.4 (2.0-3.0)
50	<50%	2+	med	68 (52-82)	1.4 (1.1-1.7)	6.0 (2.7-16.2)
50	>50%	2+	med	68 (56-78)	1.4 (1.1-1.6)	3.5 (1.9-7.4)
50	<50%	0-1	med	67 (57-76)	1.4 (1.2-1.6)	2.8 (1.7-5.2)
50	>50%	0-1	med	60 (57-63)	1.2 (1.1-1.4)	1.7 (1.4-2.0)
50	<50%	2+	high	59 (41-75)	1.2 (0.9-1.5)	3.6 (1.6-9.3)
50	>50%	2+	high	58 (45-70)	1.2 (0.9-1.4)	2.1 (1.2-4.4)
50	<50%	0-1	high	56 (46-68)	1.2 (1.0-1.4)	1.7 (1.1-3.1)
50	>50%	0-1	high	48 (45-52)	1.0	1.0



<b>Age</b>	<b>% Wash Hands</b>	<b>#Children in House</b>	<b>Village Education</b>	<b>Prevalence Rate</b>	<b>Prevalence Rate Ratio<sup>a</sup></b>	<b>Relative Odds Ratio<sup>b</sup></b>
60	<50%	2+	low	71 (54-84)	1.5 (1.2-1.9)	8.6 (3.9-22.2)
60	>50%	2+	low	71 (59-81)	1.5 (1.3-1.8)	5.0 (2.7-10.7)
60	<50%	0-1	low	71 (62-80)	1.5 (1.3-1.8)	4.1 (2.5-7.8)
60	>50%	0-1	low	66 (61-69)	1.4 (1.3-1.6)	2.4 (2.0-3.0)
60	<50%	2+	med	66 (50-81)	1.4 (1.1-1.8)	6.0 (2.7-16.2)
60	>50%	2+	med	66 (53-76)	1.4 (1.1-1.7)	3.5 (1.9-7.4)
60	<50%	0-1	med	65 (55-74)	1.4 (1.2-1.7)	2.8 (1.7-5.2)
60	>50%	0-1	med	58 (54-62)	1.3 (1.2-1.4)	1.7 (1.4-2.0)
60	<50%	2+	high	57 (39-74)	1.2 (0.9-1.6)	3.6 (1.6-9.3)
60	>50%	2+	high	55 (42-68)	1.2 (0.9-1.5)	2.1 (1.2-4.4)
60	<50%	0-1	high	54 (43-66)	1.2 (1.0-1.4)	1.7 (1.1-3.1)
60	>50%	0-1	high	46 (42-50)	1.0	1.0

<sup>a</sup> Subjects of the same age who washed hands before eating >50% of the time, who had <2 children in their household, and who lived in a village with a high education level were the referent category for all PRR calculated.

<sup>b</sup> Subjects of the same age who washed hands before eating >50% of the time, who had <2 children in their household, and who lived in a village with a high education level were the referent category for all ROR calculated.

**Table IV-13. Prevalence rate, prevalence rate ratio, and relative odds ratio of *Helicobacter pylori* infection for combinations of models according to age, percent of time washed hands before eating, number of children in the household, and source of drinking water**

Age	% Wash Hands	# Children in House	Type of Well	Prevalence Rate	Prevalence Rate Ratio <sup>a</sup>	Relative Odds Ratio <sup>b</sup>
40	<50%	2+	shallow village	70 (52-84)	1.3 (0.9-1.6)	7.0 (3.4-17.6)
40	>50%	2+	shallow village	72 (61-82)	1.3 (1.1-1.6)	3.9 (2.2-8.3)
40	<50%	0-1	shallow village	73 (63-81)	1.3 (1.1-1.6)	3.3 (1.9-6.2)
40	>50%	0-1	shallow village	68 (64-71)	1.2 (1.1-1.4)	1.8 (1.4-2.4)
40	<50%	2+	shallow private	69 (52-83)	1.2 (0.9-1.6)	4.9 (2.3-12.3)
40	>50%	2+	shallow private	68 (58-78)	1.2 (1.0-1.5)	2.7 (1.6-5.7)
40	<50%	0-1	shallow private	69 (59-78)	1.2 (1.1-1.5)	2.3 (1.3-4.3)
40	>50%	0-1	shallow private	61 (58-64)	1.1 (1.0-1.2)	1.3 (1.0-1.6)
40	<50%	2+	deep private	61 (42-78)	1.1 (0.8-1.4)	3.9 (1.9-9.4)
40	>50%	2+	deep private	61 (49-74)	1.1 (0.9-1.3)	2.2 (1.2-4.5)
40	<50%	0-1	deep private	62 (50-74)	1.1 (0.9-1.3)	1.8 (1.1-3.2)
40	>50%	0-1	deep private	55 (49-60)	1.0	1.0
50	<50%	2+	shallow village	68 (50-83)	1.3 (0.9-1.7)	7.0 (3.4-17.6)
50	>50%	2+	shallow village	70 (58-80)	1.3 (1.1-1.6)	3.9 (2.2-8.3)
50	<50%	0-1	shallow village	71 (61-80)	1.4 (1.1-1.6)	3.3 (1.9-6.2)
50	>50%	0-1	shallow village	65 (62-68)	1.3 (1.1-1.4)	1.8 (1.4-2.4)
50	<50%	2+	shallow private	66 (50-81)	1.3 (0.9-1.6)	4.9 (2.3-12.3)
50	>50%	2+	shallow private	66 (55-76)	1.3 (1.0-1.5)	2.7 (1.6-5.7)
50	<50%	0-1	shallow private	66 (57-76)	1.3 (1.1-1.5)	2.3 (1.3-4.3)
50	>50%	0-1	shallow private	58 (56-61)	1.1 (1.0-1.3)	1.3 (1.0-1.6)
50	<50%	2+	deep private	58 (39-76)	1.1 (0.7-1.5)	3.9 (1.9-9.4)
50	>50%	2+	deep private	59 (46-7)	1.1 (0.9-1.4)	2.2 (1.2-4.5)
50	<50%	0-1	deep private	59 (48-71)	1.1 (0.9-1.4)	1.8 (1.1-3.2)
50	>50%	0-1	deep private	52 (47-57)	1.0	1.0

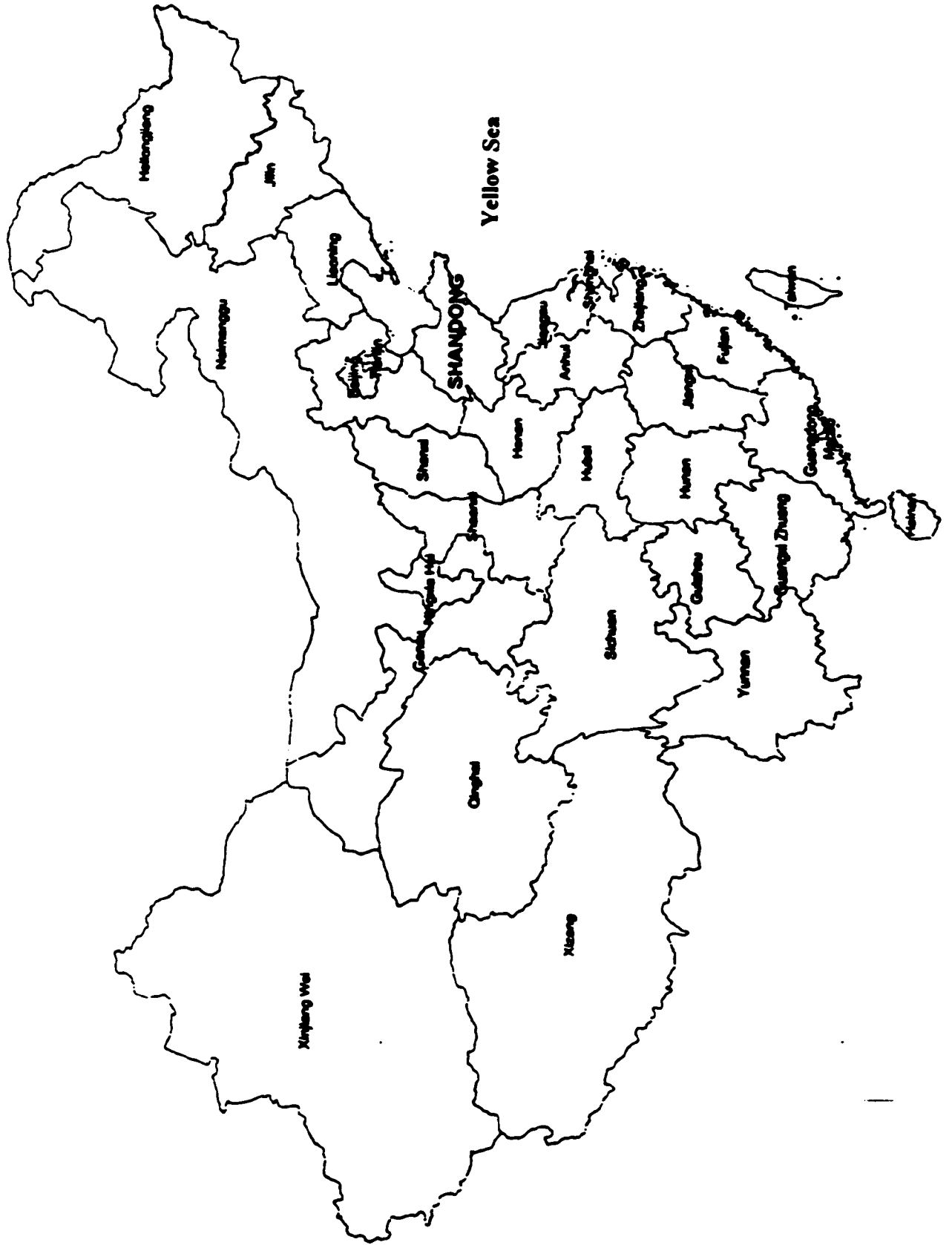
<b>Age</b>	<b>%Wash Hands</b>	<b>#Children in House</b>	<b>Type of Well</b>	<b>Prevalence Rate</b>	<b>Prevalence Rate Ratio<sup>a</sup></b>	<b>Relative Odds Ratio<sup>b</sup></b>
60	<50%	2+	shallow village	66 (47-82)	1.3 (0.9-1.7)	7.0 (3.4-17.6)
60	>50%	2+	shallow village	68 (54-78)	1.4 (1.1-1.7)	3.9 (2.2-8.3)
60	<50%	0-1	shallow village	68 (58-79)	1.4 (1.2-1.7)	3.3 (1.9-6.2)
60	>50%	0-1	shallow village	63 (59-67)	1.3 (1.1-1.4)	1.8 (1.4-2.4)
60	<50%	2+	shallow private	64 (46-79)	1.3 (0.9-1.7)	4.9 (2.3-12.3)
60	>50%	2+	shallow private	64 (52-75)	1.3 (1.0-1.6)	2.7 (1.6-5.7)
60	<50%	0-1	shallow private	64 (53-74)	1.3 (1.1-1.6)	2.3 (1.3-4.3)
60	>50%	0-1	shallow private	56 (52-59)	1.1 (1.0-1.3)	1.3 (1.0-1.6)
60	<50%	2+	deep private	56 (36-74)	1.1 (0.8-1.5)	3.9 (1.9-9.4)
60	>50%	2+	deep private	56 (42-70)	1.1 (0.9-1.4)	2.2 (1.2-4.5)
60	<50%	0-1	deep private	57 (45-68)	1.2 (0.9-1.4)	1.8 (1.1-3.2)
60	>50%	0-1	deep private	49 (43-55)	1.0	1.0

<sup>a</sup>Subjects of the same age who washed hands before eating >50% of the time, who had <2 children in their household, and whose drinking water came from a deep private well are the referent category for all PRRs.

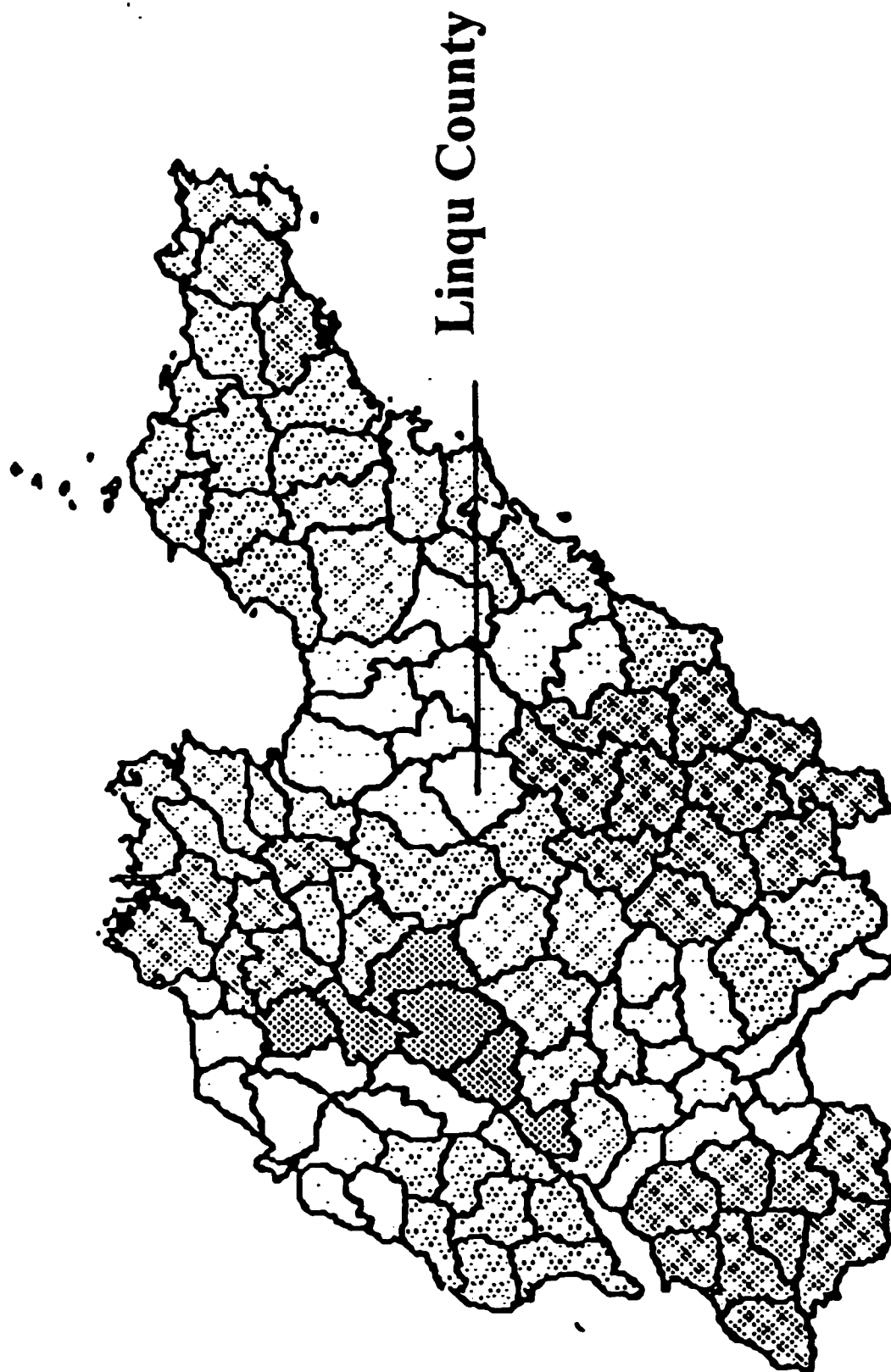
<sup>b</sup>Subjects of the same age who washed hands before eating >50% of the time, who had <2 children in their household, and whose drinking water came from a deep private well are the referent category for all RORs.

## APPENDIX 1

# CHINA



# SHANDONG PROVINCE



## APPENDIX 2

**SHANDONG INTERVENTION STUDY QUESTIONNAIRE**

Village\_\_\_\_\_

Study Subject ID\_\_\_\_\_

Sex: 1 male 2 female

Date of Birth \_\_\_\_\_  
YR MO DADate of Interview \_\_\_\_\_  
YR MO DA

Time Start Interview \_\_:\_\_

Time End Interview \_\_:\_\_

Total Time \_\_ minutes

Interviewer ID \_\_\_\_\_

**INTRODUCTION:**

Thank you for agreeing to participate in this study. During this interview, I will be asking questions about your household composition now and during childhood, your washing, smoking, drinking, and eating habits, and general background information about you and your family. Your cooperation is very important to this research study and will help us learn more about the health of adults in Linqu. I would like to remind you that your participation is voluntary and that the information you provide will be kept confidential and will be used only for research purposes.



## Section 1. Background

First, I'd like to ask a few background questions.

1.1 Are you currently (READ):

Married.....1  
 Widowed.....2 (skip to 1.4)  
 Divorced or separated, or..3 (skip to 1.4)  
 Never married.....4 (skip to 1.4)

1.2 How many years of education does your spouse have?

\_\_\_\_\_ Years  
 None.... 0

1.3 What is your spouse's current occupation?

Grain Farmer.....1  
 Fruit Farmer.....2  
 Vegetable Farmer.....3  
 Village Leader.....4  
 Not working.....5  
 Other, Specify \_\_\_\_\_

1.4 How many years of education do you have?

\_\_\_\_\_ Years  
 None.... 0

1.5 What is your current occupation?

Grain Farmer.....1  
 Fruit Farmer.....2  
 Vegetable Farmer.....3  
 Village Leader.....4  
 Not working.....5  
 Other, Specify \_\_\_\_\_

1.6 What is the total amount of income earned last year by people who live in your house?

\_\_\_\_\_ Yuan

## Section 2. - Household Composition

Now I would like to ask some questions about your current household.

- 2.1 How many people including yourself live in your house?

\_\_\_\_\_ People

- 2.2 How many children 10 years old and younger live in your house?

\_\_\_\_\_ Children

- 2.3 Do you share a bed with someone else in your household?

No.....0 (Skip to 2.5)

Yes.....1

- 2.4 Whom do you share a bed with? (Circle all that apply)

Spouse.....0

Children.....1 How many? \_\_\_\_\_

Other.....2 specify \_\_\_\_\_

- 2.5 What kind of animals live inside your house with you? (Circle all that apply)

None.....0

Cats.....1 How many? \_\_\_\_\_

Dogs.....2 How many? \_\_\_\_\_

Rabbits.....3 How many? \_\_\_\_\_

Other, specify \_\_\_\_\_

- 2.6 What kind of animals live outside your house in the court yard? (Circle all that apply)

None.....0

Dogs.....1

Pigs.....2

Sheep.....3

Ducks.....4

Cows.....5

Donkeys.....6

Cats.....7

Chickens.....8

Rabbits.....9

Goats.....10

Other, specify \_\_\_\_\_

### Section 3. Water and Personal Habits (Personal Hygiene)

Now I would like to ask some questions about your current source of water and washing habits.

3.1 What is your usual source of drinking water?

Deep private well..... 1  
 Shallow private well.....2  
 Deep village well.....3  
 Shallow village well.....4  
 Pond.....5  
 River.....6  
 Ditch.....7  
 Running water.....8

3.2 Do you store your drinking water in a jar?

No.....0 (Skip to 3.4)  
 Yes.....1

3.3 If yes, How long do you store your drinking water?

\_\_\_\_\_ Number of days

Or

\_\_\_\_\_ Number of weeks

3.4 In the summer, when you drink water, how often is it boiled?

Always.....0  
 More than half the time...1  
 Less than half the time ..2  
 Never.....3

3.5 How often are your chopsticks and bowls washed after meals?

Always.....0  
 More than half the time...1  
 Less than half the time...2  
 Never.....3 (skip to 3.8)

3.6 When your chopsticks and bowls are washed, what kind of water do you usually use?

Hot water.....0  
 Hot & cold water equally..1  
 Cold water.....2

- 3.7 When your chopsticks and bowls are washed, how often is detergent used?
- Always.....0  
 More than half the time...1  
 Less than half the time...2  
 Never.....3
- 3.8 How often is you cup washed after you use it?
- Always.....0  
 More than half the time...1  
 Less than half the time...2  
 Never.....3
- 3.9 How often do members of your family share cups?
- Always.....0  
 More than half the time...1  
 Less than half the time...2  
 Never.....3
- 3.10 How often do you wash your hands before eating?
- Always.....0  
 More than half the time...1  
 Less than half the time...2  
 Never.....3
- 3.11 How often do you wash your hands after bowel movements?
- Always.....0  
 More than half the time...1  
 Less than half the time...2  
 Never.....3
- 3.12 How often do you wash your hands before preparing food?
- Always.....0  
 More than half the time...1  
 Less than half the time...2  
 Never.....3  
 Don't prepare food.....9

3.13 How often do you use soap when you wash your hands?

Always.....0  
 More than half the time...1  
 Less than half the time...2  
 Never.....3

3.14 When it is cold outside, how many times per day, week, month, or year do you wash yourself?

\_\_\_ Times per day  
 \_\_\_ Times per week  
 \_\_\_ Times per month  
 \_\_\_ Times per year  
 \_\_\_ Never wash...997 (skip to 3.16)

3.15 When it is cold, where do you usually wash yourself?

At Home .....0  
 River.....1  
 Stream.....2  
 Pond.....3  
 Ditch.....4  
 Public Bath House.....5

3.16 When it is warm outside, how many times per day, week, month, or year do you wash yourself?

\_\_\_ Times per day  
 \_\_\_ Times per week  
 \_\_\_ Times per month  
 \_\_\_ Times per year  
 \_\_\_ Never wash...997 (skip to 3.19)

3.17 When it is warm, where do you usually wash yourself?

In the house.....0  
 In the yard.....1  
 River.....2  
 Stream.....3  
 Pond.....4  
 Ditch.....5  
 Public Bath House.....6

3.18 How often do you use soap when you wash yourself?

Always.....0  
 More than half the time...1  
 Less than half the time...2  
 Never.....3

3.19 How many times per day, week, month, or year do you spit onto the ground?

☐ Times per day  
☐ Times per week  
☐ Times per month  
☐ Times per year  
☐ Never spit...997

3.20 How many times per day, week, or month do you brush your teeth?

☐ Times per day  
☐ Times per week  
☐ Times per month  
☐ Never ....997

3.21 How often do you swim in the river or reservoir?

☐ Times per year  
☐ Never ....997

3.22 Have you ever washed diapers?

No.....0 (Skip to 3.24)  
 Yes.....1

3.23 Where did you wash the diapers?

At Home.....0  
 River.....1  
 Stream.....2  
 Pond.....3  
 Ditch.....4

3.24 How often did you feed your child (children) by prechewing their food?

Often.....0  
 Sometimes.....1  
 Never.....2

3.25 How often did you kiss your child (children) on the mouth when they were less than ten years old?

Often.....0  
 Sometimes.....1  
 Never.....2

## Section 4. Eating Habits

Now I would like to ask some questions about your eating habits and health.

- 4.1 How do you prefer the saltiness of your food? Do you prefer lightly salty, moderately salty, or very salty?

Lightly salty.....1  
 Moderately salty.....2  
 Very salty.....3

- 4.2 Do you eat sour pancake?

Yes.....1  
 No.....0 (Skip to 4.3)

For how many months did you eat sour pancake last year? \_\_\_\_\_ Months

On average how many days per month did you eat it? \_\_\_\_\_ Days

On average how many Lian did you eat per day? \_\_\_\_\_ Lian

- 4.2 Do you eat sweet pancake?

Yes.....1  
 No.....0 (Skip to 4.4)

For how many months did you eat sweet pancake last year? \_\_\_\_\_ Months

On average how many days per month did you eat it? \_\_\_\_\_ Days

On average how many Lian did you eat per day? \_\_\_\_\_ Lian

- 4.4 How many times per day, week, month, or year do you eat raw fruits or vegetables in season?

\_\_\_\_\_ Times per day  
 \_\_\_\_\_ Times per week  
 \_\_\_\_\_ Times per month  
 \_\_\_\_\_ Times per year  
 Never eat ..997 (Skip to 4.7)

- 4.5 How often are your raw fruits and vegetables washed before you eat them?

Always.....0  
 More than half the time...1  
 Less than half the time...2  
 Never.....3

4.6 How often are your raw fruits and vegetables peeled before you eat them?

Always.....0  
More than half the time...1  
Less than half the time...2  
Never.....3

4.7 How many times per day, week, month, or year do you have gastric reflux?

\_\_\_ Times per day  
\_\_\_ Times per week  
\_\_\_ Times per month  
\_\_\_ Times per year  
Never have reflux ..997



## Section 5. Smoking and Drinking Habits

Now I would like to ask some questions about your smoking and drinking habits.

5.1 Did you ever smoke cigarettes?

No.....0 (Skip to 5.6)

Yes.....1

5.2 How old were you when you started smoking?

\_\_\_\_\_ years old

5.3 Do you currently smoke cigarettes?

No.....0

Yes.....1

5.4 How many cigarettes do (did) you usually smoke each day?

\_\_\_\_\_ cigarettes per day

5.5 How many years have you smoked (did you smoke) cigarettes?

\_\_\_\_\_ number of years

5.6 Did you ever drink alcoholic beverages?

No.....0 (Skip to Section 6)

Yes.....1

5.7 How old were you when you started drinking alcoholic beverages?

\_\_\_\_\_ years old

5.8 Do you currently drink alcoholic beverages?

No.....0

Yes.....1

5.9 How many times do (did) you usually drink each week?

\_\_\_\_\_ times per week

5.10 How many years have you drunk (did you drink) alcoholic beverages?

\_\_\_\_\_ number of years

## Section 6. Childhood Household Composition

Now I would like to ask some questions about your household when you were a child.

6.1 When you were 10 years old, what kind of floor did your house have?

Cement.....0  
 Brick.....1  
 Ground.....2  
 Other, specify \_\_\_\_\_

6.2 When you were 10 years old, how many people including yourself, lived in your house?

\_\_\_\_\_ People

6.3 When you were 10 years old, how many brothers and sisters did you have?

\_\_\_\_\_ siblings  
 (If none skip to 6.5)

6.4 What were the ages of your brothers and sisters when you were 10 years old?

\_\_\_\_\_ years old  
 \_\_\_\_\_ years old  
 \_\_\_\_\_ years old  
 \_\_\_\_\_ years old  
 \_\_\_\_\_ years old

5 When you were 10 years old, what kind of animals lived inside your house with you?  
 (Circle all that apply)

None.....0  
 Cats.....1 How many? \_\_\_\_\_  
 Dogs.....2 How many? \_\_\_\_\_  
 Rabbits...3 How many? \_\_\_\_\_  
 Other, specify \_\_\_\_\_

6.6 When you were 10 years old, how many people did you share a bed with?

\_\_\_\_\_ People

6.7 When you were 5 years old, how many people did you share a bed with?

\_\_\_\_\_ People

6.8 When you were a small child, how often did your parents prechew your food for you?

Often.....0

Sometimes.....1

Never.....2

Don't know.....9

6.9 When you were a small child, how often did your parents kiss you on the mouth?

Often.....0

Sometimes.....1

Never.....2

Don't know.....9

I have nothing else to ask today. Thank you for answering my questions. The information you have given us is very important.

## Interviewer Comments

1. The subject's cooperation was:

Very Good.....1  
 Good.....2  
 Fair.....3  
 Poor.....4

2. The overall quality of this interview is:

High Quality.....1  
 Generally Reliable....2  
 Questionable.....3  
 Unsatisfactory.....4

3. The main reason(s) for the unsatisfactory or questionable quality is (are) that the subject  
 (Code all that apply)

Was too .....01  
 Had poor hearing, or speech.....02  
 Was evasive or suspicious.....03  
 Was upset or depressed.....04  
 Was bored or disinterested.....05  
 Did not understand the questions..06  
 Could not remember events well....07  
 Was confused or disoriented.....08  
 Other, Specify\_\_\_\_\_

4. How many individuals besides the study subject were present during the interview?

\_\_\_\_\_ Number present

5. Who was present during the interview? (Circle all that apply)

Spouse.....1  
 Mother.....2  
 Father.....3  
 Daughter.....4    How many? \_\_\_\_\_  
 Son.....5    How many? \_\_\_\_\_  
 Other, specify\_\_\_\_\_

## INFORMED CONSENT

Subject I.D. number:

### Purpose of the Research

In order to improve the people's health, the Beijing Institute for Cancer Research, the Weifang Medical Institute, and the Linqu Bureau of Health in collaboration with the United States National Cancer Institute are initiating a medical research trial among individuals like yourself who participated in earlier medical examinations. The study will help us to test the effectiveness of several treatments in fighting the high rate of stomach cancer in Linqu. You are invited to join this 42-month research study.

### What is Involved

The study involves taking three types of active treatment or placebo, answering some questions, having samples of your blood and breath collected, and having a gastroscopic examination.

#### 1. Treatments:

One treatment involves an antibiotic medication to help cure a bacterial infection that occurs in the stomach and that may increase risk of stomach cancer. Another is a garlic supplement, and a third is a vitamin/mineral supplement. The treatments involve taking 3 capsules before the morning meal and 3 before the evening meal. Bottles containing each type of capsule (either the active ingredient or a placebo) will be distributed monthly. The study will be "blinded" in that we will not know which combinations of the active treatments you will be taking until the trial is over (unless there is a medical need to know the treatment). This helps ensure the scientific validity of the trial. One in eight participants will receive only placebo.

#### 2. Information Collection:

You will also be given a short questionnaire at the time of enrollment into the trial and at months 12, 24, and 42 to collect basic information on health and lifestyle factors.

#### 3. Blood Collections:

At months 12, 24, and 42 you will be asked to have 5 ml of blood taken from your arm. This blood will be used to determine the effect of treatment on bacteria, and some will be stored for later studies related to this project. Every three months we will ask 60 different randomly selected participants to have 10 ml of blood taken from their arm to measure nutrients and garlic compounds, which can be used to assess pill-taking compliance.

#### 4. Breath Collections:

At about 3 and 6 months into the trial, you will be asked to take a teaspoon of a liquid containing natural protein byproducts and to breathe into a tube or bag. Your breath will be used to assess the effectiveness of treatment for bacteria. A randomly selected group of 200 participants will be asked to have their breath collected at months 12, 24, and 42.

#### 5. Gastroscopic Examination:

After 42 months, you will be asked to have another gastroscopic examination like you have had before. This exam, done by a skilled gastroenterologist, will tell us whether the pills you have been taking have helped improve stomach conditions.

### Risks

There is only minimal risk to you in participating in this research study. Vitamin and mineral supplements and the ingredients in the garlic preparation are widely available around the world. There is very little evidence of toxicity associated with these agents. A pilot study in one of our 14 villages revealed no serious side-effects. There are also no known side-effects associated with the breath test.

The treatment for bacteria (amoxicillin/omeprazole), however, has been associated with side effects in some cases. The most common symptoms observed in the pilot study in Linqu were diarrhea (13%), rashes (8%), and abdominal bloating (5%). Also reported were a few complaints of constipation and nausea. In rare instances a sore mouth can result, and in extremely rare instances more severe reactions can occur. Please tell us if you have had allergic reactions, such as skin rashes to drugs in the past. Also, if you enroll in the trial, please tell us if any of these symptoms (especially rashes) develop during the trial.

Blood drawing may cause a small amount of pain when the needle is passed into the vein, but should not cause long term pain. After blood is taken sometimes there can be a small bruise or soreness at the site.

While there have been no serious complications in over 8000 gastroscopic procedures of this type, there is a very small chance that bleeding may occur. You will be instructed how to detect and treat such problems.

### Benefits

If you agree to participate you will become part of a research study which may help us understand more about this bacterial infection and about garlic and vitamin supplements and whether the treatments may lower the risk of changes in the stomach that could lead to cancer. You also may benefit by having your health monitored closely and possibly having stomach cancer diagnosed at an early, potentially curable stage.

### Confidentiality of Records

The results of the study we are conducting will be reported in medical journals or at scientific meetings, but we will very carefully keep and handle the records of the study to ensure that your identification will not be made public.

### Participation Is Voluntary

You must volunteer to be in the study. You will not be paid for being in the study, and if you want to leave the study at any time, you can and you will still be able to receive medical care.

If you refuse to be in the study, there will be no penalty or loss of your usual benefits to which you are otherwise entitled and you may discontinue your participation in the study at any time without penalty or loss of your otherwise entitled benefits. Nonparticipation will not effect your relationship with the Linq Health Bureau and you will also be able to take advantage of future activities which the Beijing Institute for Cancer Research may conduct in Linq.

### Who to Contact with Questions

If you have any questions you can contact \_\_\_\_\_ in your village or any of the persons doing the study.

I understand the information about the study that is contained in the consent form and it has been discussed with me. I have had all my questions answered. I hereby consent to take part in the study.

\_\_\_\_\_  
Signature or Fingerprint of Adult Participant

\_\_\_\_\_  
Date Signed

I administered the informed consent and believe that the study subject understands the purpose of the study and the possible risks and benefits.

\_\_\_\_\_  
Signature of BICR Field Staff

\_\_\_\_\_  
Date Signed

# 山东干预试验研究问卷调查表

村庄:\_\_\_\_\_ 组号\_\_\_\_\_ 研究对象编号(ID):\_\_\_\_\_

姓名:\_\_\_\_\_ 性别:1.男 2.女 出生日期\_\_\_\_年\_\_\_\_月

调查日期:\_\_\_\_年\_\_\_\_月\_\_\_\_日 调查开始时间:\_\_\_\_\_ 调查结束时间:\_\_\_\_\_ 总计时间:\_\_\_\_\_分

调查员编号:\_\_\_\_\_ 调查员签字:\_\_\_\_\_

## 介绍:

谢谢您同意参加这项研究.这次调查(访问)我将问您以下问题:您现在及儿童时期的家庭成员,您的刷牙、吸烟、饮酒及饮食习惯,您及您家庭的基本情况。您的合作对这次调查研究非常重要,将有助于我们更多地了解临朐县成年人的健康问题。我想提醒您,您的参与是自愿的,您提供的信息(内容)我将予以保密,并仅用于研究。

## 第一部分 基本情况

我先问您几个基本问题:

1.1 您现在的婚姻状况如何?

在婚……………1

丧妻或丧夫…2(跳到 1.4)

离婚或分居…3(跳到 1.4)

从未…4(跳到 1.4)

1.2 您配偶上过几年学? \_\_\_\_\_年

没上过学…0

1.3 您配偶目前从事什么工作?

粮农……………1

果农……………2

菜农……………3

村干部…………4

没工作…………5

其它,具体说明\_\_\_\_\_

1.4 您上过几年学?

\_\_\_\_\_年

没上过学…0

1.5 您现在从事什么工作?

粮农……………1

果农……………2

菜农……………3

村干部…………4



其它,具体说明\_\_\_\_\_

1.6 去年您全家总共收入多少钱? \_\_\_\_\_元

**第二部分 家庭情况**

现在我想问您目前的家庭情况

2.1 您家有几口人(包括您在内)? \_\_\_\_\_人(如只有1人,跳到2.5)

2.2 您家10岁及以下的孩子有几个? \_\_\_\_\_个

2.3 在家里您与别人合用一张床吗?

不……0(跳到2.5)

是……1

2.4 您与谁合用一张床?(在相应符号上划圈)

配偶……0

孩子……1 几个\_\_\_\_\_?

其它……2 具体说明\_\_\_\_\_

2.5 您家屋内养有什么动物?(在相应的符号上划圈)

无……0

猫……1 几只\_\_\_\_\_

狗……2 几只\_\_\_\_\_

兔子……3 几只\_\_\_\_\_

其它,具体说明\_\_\_\_\_

2.6 您家院内养有什么动物?(在相应符号上划圈)

无……0

狗……1

猪……2

绵羊……3

鸭……4

牛……5

驴……6

猫……7

鸡……8

兔子……9

山羊……10

其它,具体说明\_\_\_\_\_

**第三部分 饮水和个人习惯(个人卫生)**

3.1 您平时饮用什么水?

私人深井……1

私人浅井……2

村里深井.....3  
 村里浅井.....4  
 池塘.....5  
 河水.....6  
 沟渠.....7  
 自来水.....8

3.2 您将饮用水存在缸里吗?

不.....0(跳到 3.4)

是.....1

3.3 如是,您把水存放多长时间? \_\_\_\_\_天,或\_\_\_\_星期

3.4 在夏天,饮用开水的情况如何?

总是.....0

多半时间是.....1

多半时间不是.....2

从不.....3

3.5 饭后碗筷刷洗情况如何?

总是洗.....0

多半洗.....1

多半不洗.....2

从不洗.....3(跳到 3.8)

3.6 您家用什么水洗碗筷?

热水.....0

热水凉水各半.....1

凉水.....2

3.7 您家刷洗碗筷时使用洗洁剂吗?

总是.....0

多半是.....1

多半不是.....2

从来不.....3

3.8 您家的茶杯用后洗刷吗?

总是.....0

多半是.....1

多半不是.....2

从来不.....3

3.9 您家的茶杯合用吗?

总是.....0

多半是.....1

多半不是.....2

从来不.....3

3.10 您饭前洗手吗?

总是.....0

多半是.....1

多半不是.....2

- 3.11 您便后洗手吗? 从不.....3
- 总是.....0  
多半是.....1  
多半不是.....2  
从不.....3
- 3.12 您做饭之前洗手吗?
- 总是.....0  
多半是.....1  
多半不是.....2  
从不.....3  
不做饭.....9
- 3.13 您洗手时用肥皂吗?
- 总是.....0  
多半是.....1  
多半不是.....2  
从不.....3
- 3.14 当气温变冷时,您多长时间洗一次澡?
- \_\_\_\_\_次/天  
\_\_\_\_\_次/周  
\_\_\_\_\_次/月  
从不.....997(跳到 3.16)
- 3.15 天冷时,您一般在哪儿洗澡? 屋里.....0  
江河.....1  
小河.....2  
池塘.....3  
沟渠.....4  
浴池.....5
- 3.16 当气温暖和时,您多长时间洗一次澡?
- \_\_\_\_\_次/天  
\_\_\_\_\_次/周  
\_\_\_\_\_次/月  
从不.....997(跳到 3.19)
- 3.17 天暖时,您一般在哪儿洗澡? 屋里.....0  
院子里.....1  
江河.....2  
小河.....3  
池塘.....4  
沟渠.....5  
浴池.....6
- 3.18 您洗澡时用肥皂吗?
- 总是.....0  
多半是.....1  
多半不是.....2

3.19 您随地吐痰吗?

\_\_\_\_\_次/天  
 \_\_\_\_\_次/周  
 \_\_\_\_\_次/月  
 从不.....997

3.20 您刷牙吗?

\_\_\_\_\_次/天  
 \_\_\_\_\_次/周  
 \_\_\_\_\_次/月  
 从不.....997

3.21 您常在河里或水库里游泳吗?

\_\_\_\_\_次/年  
 从不.....997

3.22 您洗过婴儿的尿布吗?

不.....0(跳到 3.24)  
 是.....1

3.23 您在什么地方洗婴儿尿布?

家里.....0  
 江河.....1  
 小河.....2  
 池塘.....3  
 沟渠.....4

3.24 您经常将食物嚼烂喂婴儿吗?

经常.....0  
 有时.....1  
 从不.....2

3.25 您经常口对口亲吻您的孩子(10岁以下)吗?

经常.....0  
 有时.....1  
 从不.....2

#### 第四部分 饮食习惯

现在我想问您一些有关饮食和健康的问题

4.1 您喜欢吃咸还是淡? 淡.....1  
 中等.....2  
 咸.....3

4.2 您吃酸煎饼吗? 是.....1

不.....0(跳到 4.3)

去年一共吃了几个月的酸煎饼? \_\_\_\_\_月  
 平均一个月吃几天? \_\_\_\_\_天  
 平均一天吃几两? \_\_\_\_\_两

4.3 您吃甜煎饼吗? 是.....1

不……0(跳到 4.4)

去年一共吃了几个月的甜煎饼? \_\_\_\_\_ 月

平均一个月吃几天? \_\_\_\_\_ 天

平均一天吃几两? \_\_\_\_\_ 两

4.4 您生吃水果或蔬菜吗?

\_\_\_\_\_ 次/天

\_\_\_\_\_ 次/周

\_\_\_\_\_ 次/月

\_\_\_\_\_ 次/年

从不吃……997(跳到 4.7)

4.5 生吃水果或蔬菜前常洗吗?

总是……0

多半是……1

多半不是……2

从来不……3

4.6 生吃水果或蔬菜前常削皮吗?

总是……0

多半是……1

多半不是……2

从来不……3

4.7 您有没有过胃内返酸?

\_\_\_\_\_ 次/天

\_\_\_\_\_ 次/周

\_\_\_\_\_ 次/月

\_\_\_\_\_ 次/年

从没有过……997

## 第五部分 吸烟和饮酒习惯

现在我想问一下您的吸烟与饮酒情况

5.1 您吸过卷烟吗?

否……0(跳到 5.6)

是……1

5.2 您几岁开始吸烟? \_\_\_\_\_ 岁

5.3 目前您还吸卷烟吗?

否……0

是……1

5.4 通常您一天吸几支烟? \_\_\_\_\_ 支/天

5.5 您的吸烟史有多长? \_\_\_\_\_ 年

5.6 您有饮酒史吗?

无……0(跳到第 6 部分)

有……1

5.7 您几岁开始饮酒? \_\_\_\_\_ 岁

5.8 现在您还饮酒吗?

不.....0

是.....1

5.9 通常您一周饮几次酒? \_\_\_\_\_次/周

5.10 您的饮酒史有多长? \_\_\_\_\_年

### 第六部分 童年时的家庭情况

现在我想问您小时候家庭的一些情况

6.1 您 10 岁时,家里的地面是用什么铺成的?

水泥.....0

砖.....1

土.....2

其它,具体说明 \_\_\_\_\_

6.2 您 10 岁时家里有几口人?(包括您在内)\_\_\_\_\_人

6.3 您 10 岁时兄弟姐妹几个(不包括您本人)? \_\_\_\_\_人

(如没有,跳到 6.5)

6.4 您 10 岁时他(她)们分别几岁?(已婚的要注明)

_____	_____	岁
_____	_____	岁
_____	_____	岁
_____	_____	岁
_____	_____	岁

6.5 您 10 岁时,您屋内养有什么动物?(在相应符号上划圈)

无.....0

猫.....1 \_\_\_\_\_只

狗.....2 \_\_\_\_\_只

兔子.....3 \_\_\_\_\_只

其它,具体说明 \_\_\_\_\_

6.6 您 10 岁时,几人与您同用一张床? \_\_\_\_\_人

6.7 您 5 岁时,几人与您同用一张床? \_\_\_\_\_人

6.8 您小时候父母经常将食物嚼烂后喂您吗?

经常.....0

有时.....1

从不.....2

不知道...997

6.9 您小时候您父母口对口亲吻过您吗?

经常.....0

有时.....1

从不.....2

不知道...997

我问完了,谢谢您回答我的问题,您给我们提供的情况很重要。

调查对象的合作情况：  
 很好.....1  
 好.....2  
 可以.....3  
 不好.....4

这次调查的质量：  
 质量高.....1  
 一般可靠.....2  
 可能有问题.....3  
 不能令人满意.....4

可能有的问题或令人不满意的原因(在所有的原因符号上划圈)

病重.....01  
 听力不行或口齿不清...02  
 推诿或多疑.....03  
 心烦或压抑.....04  
 无聊或不感兴趣.....05  
 听不懂问话.....06  
 记忆不好.....07  
 拒绝或不配合.....08  
 其它,具体说明\_\_\_\_\_

除调查对象外,调查时还有几人在场? \_\_\_\_\_人

有谁在场?(在相应的符号上划圈)

配偶.....1  
 母亲.....2  
 父亲.....3  
 女儿.....4 \_\_\_\_\_人  
 儿子.....5 \_\_\_\_\_人  
 其它,具体说明\_\_\_\_\_

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